VOLUME 48 NUMBER 4 APRIL 1955

DOES NOT CIRCULATE

PROCEEDINGS *of the* ROYAL SOCIETY OF MEDICINE

UNIVERSITY OF MICHIGAN
JUN 7 1955
MEDICAL LIBRARY

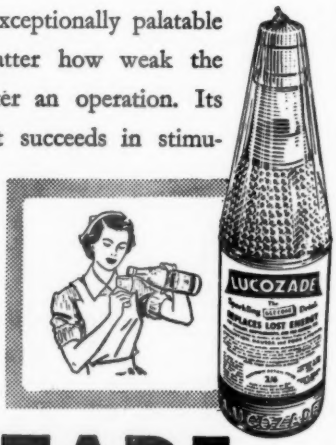
Published for
THE ROYAL SOCIETY OF MEDICINE, 1 WIMPOLE STREET, LONDON, W.1
by
H. K. LEWIS & Co. LTD., 136 GOWER STREET, LONDON, W.C.1
In U.S.A., GRUNE & STRATTON, INC., 381, FOURTH AVENUE, NEW YORK CITY
Monthly, 10s. 6d. net Annual Subscription, £6 6s. in the British Commonwealth, $19.00 in the U.S.A.
All rights reserved

Not everybody will take Glucose

...so often it is unacceptable to a patient ...particularly when the stomach is in a weakened state.

but everybody can drink Lucozade

Here is Glucose in an exceptionally palatable form—acceptable no matter how weak the patient may be, even after an operation. Its flavour never cloys—but succeeds in stimulating the appetite. Altogether it is a most valuable drink and one of which the medical profession is making full use.



LUCOZADE

the sparkling glucose drink

REPLACES LOST ENERGY

Section of Surgery

President—HAROLD C. EDWARDS, C.B.E., M.S., F.R.C.S.

[*December* 1, 1954]

DISCUSSION ON TOXIC AND NUTRITIONAL DISTURBANCES IN THE SMALL INTESTINE ASSOCIATED WITH SURGERY OF THE GASTRO-INTESTINAL TRACT

Mr. John Bruce:

There is evidence of a growing recognition that serious structural and functional derangement of the small intestine may follow operations for disease elsewhere, and especially in the abdomen. Many of these disturbances are still relatively mysterious; the circumstances under which they arise may be appreciated, but the mechanisms which evoke them are obscure. For this reason an acceptable classification is scarcely possible, but the following catalogue drawn up along with Professor Ian Aird may provide a basis for discussion (Table I).

TABLE I.—DISORDERS OF THE SMALL INTESTINE FOLLOWING GASTRO-INTESTINAL SURGERY

A. DISORDERS OF MOTILITY
- (1) *Small bowel obstruction*
  - (A) Paralytic
  - (B) Toxic (peritonitic)
  - (C) Mucosal œdema of jejunum after gastrectomy
- (2) *Exaggerated motility*
  - (A) Early diarrhœa following gastric operations
  - (B) Late „ „ „ „

B. POST-OPERATIVE NECROSIS OF THE MUCOUS MEMBRANE
(Acute pseudomembranous or necrotizing enteritis)

C. DISORDERS OF DIGESTION AND ABSORPTION
- (A) Jejuno-ileal insufficiency following massive resections of gut
- (B) Blind loop or "cul-de-sac" syndrome
- (C) Chronic intestinal hurry
  - (1) Following gastrectomy
  - (2) Following gastro-jejuno-colic fistula
- (D) Loss of digestive juices from biliary, pancreatic or intestinal fistulæ

I propose to leave the consideration of post-operative obstructions to Professor Ian Aird, and to concentrate first on some aspects of increased small bowel activity immediately following gastric surgery.

Diarrhœa after gastrectomy.—Mild and transient diarrhœa is not uncommon a few days after gastrectomy. It is usually ascribed to jejunal irritation by ingested organisms, which now escape destruction in consequence of the diminished acidity of the gastric juice; though it is seldom possible to demonstrate pathogenic organisms in the fæces. Howie *et al.* (1953) have suggested that the migration into the stomach and upper reaches of the intestine of organisms normally resident lower down is a more likely cause.

Reduced gastric acidity, with consequent bacterial proliferation in the upper jejunum, is also suspect in diarrhœa following vagotomy. Commonly this is more troublesome than post-gastrectomy diarrhœa; indeed, in some 20% of patients it is severe, and it may run a protracted course, or recur repeatedly after intervals of freedom. Other factors than hyper-acidity may well contribute to its production—for example, the gastric retention, or the reduced flow of pancreatic juice that normally follows vagotomy. The speedy relief by Mecholyl suggests that gastric stasis plays some part; and I have known long-standing diarrhœa following vagotomy to be abolished by the later establishment of a gastro-enterostomy.

Perhaps the greatest importance of these simple diarrhœas is to foster an attitude of watchfulness in the post-operative period.

More often than not without serious import, diarrhœa forty-eight hours after operation may be the first evidence of a fulminating necrosis of the intestinal mucosa, one of the less common but more catastrophic of the hazards of major surgery.

Post-operative necrosis of the intestinal mucous membrane.—The clinical and pathological features of this strange condition are characteristic. A cholera-like diarrhœa begins abruptly —or, in cases undergoing suction, the aspirate becomes foul and alarmingly excessive—and collapse and peripheral circulatory failure follow so rapidly that death may occur in forty-eight to seventy-two hours, or sooner.

The striking morbid change is a diffuse or patchy necrosis of the mucous membrane of the jejunum, or ileum, or colon, or all three; the necrotic mucosa may be shed, or may form a "pseudomembrane" over the deeper layers of the bowel wall. Both to the naked eye and microscopically (Fig. 1) there is a striking absence of the recognized evidences of infection or inflammation, or of obstruction of the main intestinal vessels.

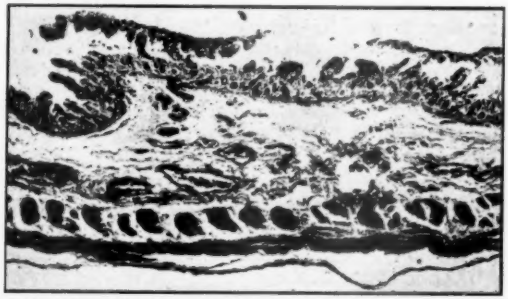


FIG. 1.—Necrotizing enteritis: Jejunum (H. and E. × 9) to show the pseudomembrane, mucosal destruction, the congestion and œdema of the submucosa and the relative integrity of the muscular and peritoneal coats.

The cause of the necrosis is by no means clear. Penner and Bernheim (1939) suggested that it was a sequel to intensive vasoconstriction of the intestinal vessels from shock. The observations of Chambers and Zweifach (1944) on the behaviour of the splanchnic circulation in experimental shock, and Grayson's (1949) striking demonstration of the extreme lability of the mucosal circulation, also give some support to an ischæmic mechanism; but what the factors are that determine an intestinal locus for such gross effects are quite unknown.

Through the co-operation of my colleagues, I have now records of 12 cases; but only in 5 had there been a distinct period of hypotension; in the rest, blood pressure recordings had not been made.

I believe this is an important entity; and evidence is accumulating that it is more common than we suppose. There have been recent reports of 107 cases from the Mayo Clinic (Pettet *et al.*, 1954); of 10, all following gastric surgery, from St. Thomas's Hospital (Williams and Pullan, 1953); and I know of instances in the practice of several of my surgical friends.

An epidemic form of primary necrotizing enteritis which has many points of resemblance was reported from Germany by Fick in 1947, and sporadic cases have occurred in this country. In certain of the German cases a Clostridium of the *welchii* type was isolated. It elaborates a powerful toxin, and it has been suggested that, acting as a chemical irritant, this causes corrosion of the mucosa, and death in consequence of the enormous outpouring of fluid.

It would be tempting, in the light of Howie's discovery of the same Clostridium in the gastric pouch, and presumably its presence also in the jejunum, to advance a similar explanation for post-operative necrosis, if it occurred only after gastrectomy. Unfortunately this is not so.

Thus, in the recent Mayo Clinic report, nearly half the patients had had operations on the colon, and some had undergone procedures outwith the abdomen—thyroidectomy, mastectomy, and even for cerebellar tumour, and it is difficult to explain how a lethal change in the intestinal flora could be brought about in these circumstances.

A fulminating necrotic enteritis may also complicate antibiotic therapy (Reiner *et al.*, 1952; Dearing and Heilman, 1953), and especially the exhibition of Aureomycin and Terramycin. It seems to be due to a resistant staphylococcus; but post-operative necrosis was well known before the antibiotic era, and, in my own cases, only one had been treated with Terramycin.

The intensity of the accompanying collapse is related to the enormous loss of fluid, electrolyte, and protein from the bowel; and, as in Asiatic cholera, early diagnosis and the heroic use of fluids, plasma and blood should improve the prognosis. Regeneration of the bowel lining is theoretically possible; for even in extreme cases, islands of mucous membrane persist at the bottom of the intestinal glands, and despite the wholesale destruction, cells may be discovered in mitotic division.

Disorders of digestion and absorption.—Post-operative malabsorption states are among the most distressing of the sequelæ of gastro-intestinal surgery. Certain of the therapeutic problems involved—such as the maintenance of fluid, electrolyte and nutritional status in the presence of intestinal and other fistulæ, and the management of the nutritional aftermath of gastrectomy—have been extensively studied of late years.

It is becoming all too apparent also that short-circuiting anastomoses are treacherous, and I have lately been concerned with 2 patients in whom a serious deficiency state arose when a Polya gastrectomy was made some years after duodeno-jejunostomy for duodenal ileus. In the first the duodeno-jejunal anastomosis was undone, and the Polya converted to a Billroth I gastrectomy, in which the blind loop was undone, with complete relief of all symptoms; the second is still under treatment.

But the problem which is of outstanding practical importance and interest to the surgeon is that of "extensive resection of the small intestine".

The length of small intestine which it is permissible to remove in extensive disease is disputed; but it is usually determined by the pathological limits of the disease. In any event, it is obviously more important to think in terms of the length of the intestine left behind. The size of the relaxed bowel after resection is a poor guide to its effective length during life; and there is such wide variation in the size of the small intestine, that measurement of a resected specimen is an inaccurate index of the amount remaining. Thus, Treves found that even in the cadaver the length of the small intestine varied between limits of 15½ and 31½ feet.

In a patient aged 47, an extensive resection, reputedly 8 feet, had been carried out for gangrenous internal strangulation. Her "intestinal size", estimated by swallowing a thread, was 5 ft. 11 in. from mouth to anus, and the barium meal illustrates how little of the intraperitoneal bowel remains (Fig. 2).

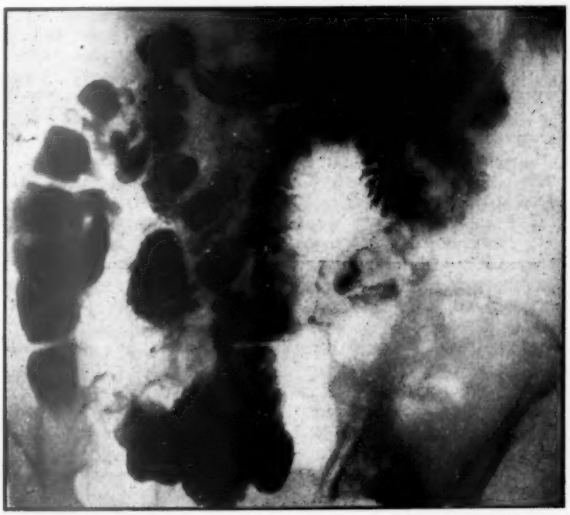


FIG. 2.—Jejuno-ileal insufficiency: Barium meal after resection of small intestine to show intestinal hurry and the extent of small intestine remaining.

After many vicissitudes she now lives in moderately good health, but on a suitably reinforced diet. She illustrated three important and common features of the "malabsorption syndrome" following extensive resection:

(1) *Its late onset.* Some three and a half years elapsed before she had serious nutritional difficulty. It is this delayed onset that makes short-term follow-up valueless and misleading.

(2) *The completeness of the malabsorption.* It has been claimed that following extensive resection the protein deficiency, the œdema, the macrocytic anæmia, and the hypocalcæmic osteoporosis which are features of the "loop" syndromes do not occur; but in this case there was every conceivable defect, including crush fractures of the spine.

(3) *The therapeutic possibilities*, provided the remaining gut is normal.

It is commonly stated that resection of up to a half of the small intestine is permissible, and up to three-quarters is generally satisfactory, with only occasional diarrhœa, provided the diet is fortified; but there is an important element of unpredictable and individual variation, and in some cases regional ileitis; for example, a latent change in the mucosa of the remaining intestine may make the nutritional problem insoluble, even in resections of less than half of the small gut.

REFERENCES

CHAMBERS, R., and ZWEIFACH, B. W. (1944) *Amer. J. Anat.*, **75**, 173.

DEARING, W. H., and HEILMAN, F. R. (1953) *Proc. Mayo Clin.*, **28**, 121.

FICK, K. A. (1947) *Z. ges. inn. Med.*, **2**, 447.

GRAYSON, J. (1949) *J. Physiol.*, **109**, 439.

HOWIE, J. W., DUNCAN, I. B. R., and MACKIE, L. M. (1953) *Lancet*, i, 1018.

PENNER, A., and BERNHEIM, A. I. (1939) *Arch. Path.*, **27**, 966.

PETTET, J. D., BAGGENSTOSS, A. H., DEARING, W. H., and JUDD, E. S., Jr. (1954) *Surg. Gynec. Obstet.*, **98**, 546.

REINER, L., SCHLESINGER, M. J., and MILLER, G. M. (1952) *Arch. Path.*, **54**, 39.

WILLIAMS, M. R., and PULLAN, J. M. (1953) *Lancet*, i, 1013.

Professor L. J. Witts:

Defective absorption of iron and vitamin B_{12} is one of the inevitable consequences of loss of the stomach in man (ReMine and Priestley, 1952; Callender *et al.*, 1954). When the gastric operation is less than a total ablation, a large number of variables is introduced which may affect the issue. Some of these are the sex and age of the patient, the amount of stomach removed, the preservation of the pyloric outlet, the length of the afferent loop, and the duration of time since the operation. To analyse these fully would demand many cases and a statistical technique akin to the Latin square. In individual patients a large number of methods of investigation is available. We can study the gastric remnant by biopsy and by the estimation of uropepsinogen in the urine, which seems the most reliable method of assessing the gastric secretion after operation. We can determine the absorption of fat by measuring the intake and output, and we can determine the absorption of iron and vitamin B_{12} by giving radioactive tracer doses of these substances. We can also determine the level of iron and vitamin B_{12} in the serum.

Pernicious anæmia is rare after partial gastrectomy or gastro-enterostomy; Wells and MacPhee (1954) give an incidence of 2 in 500 of their patients who had undergone partial gastrectomy. J. R. Evans and others in my Department have recently studied one patient with megaloblastic anæmia after gastro-enterostomy and 5 with megaloblastic anæmia after partial gastrectomy. 4 of the latter had had a Polya operation and one a high Billroth; in none was the gastrectomy total. In 5 patients we believe that the original ulcer was gastric, in one the site is not known. Anæmia developed from two to seventeen years after operation and was of the classical Addisonian type in 4 patients. In the fifth it was relatively mild. The sixth patient had a general malabsorption syndrome, the marrow was never very megaloblastic, and the anæmia was dimorphic and refractory to treatment by vitamin B_{12} and folic acid alone. The amount of uropepsinogen excreted in the urine was usually in the pernicious anæmia range, fat excreted in the stools ranged from 4 to 16% of the intake, and there was a failure to absorb vitamin B_{12}, which could be corrected by the administration of intrinsic factor, except in the patient with the malabsorption syndrome. It seems, therefore, that in 5 of these patients the megaloblastic anæmia was due to atrophic gastritis in the stomach remnant and consequent loss of intrinsic factor, while in the sixth the syndrome of jejunal insufficiency had developed as a result of the disturbance in the mechanics of the gut.

Our experience is thus a little different from that of Naish and Capper (1953) who reported 4 cases of jejunal insufficiency with steatorrhœa, œdema and anæmia after gastro-enterostomy or the Polya operation. In their patients it was shown either that the gastric juice was normal or that the syndrome could be relieved by restoring the normal continuity of the gut. In all 4 the syndrome appears to have been due to the presence of a by-passed loop of intestine. It would therefore appear that megaloblastic anæmia after gastric operations may be due either to atrophic gastritis, when it is on all fours with the classical pernicious anæmia, or

to the syndrome of the stagnant loop, in which it is combined with symptoms of jejunal insufficiency and may be relieved by restoring the continuity of the gut.

In hypochromic anæmia after gastric operations, on the other hand, less weight than formerly is now given to the loss of the gastric secretion. It is believed that iron is preferentially absorbed in the duodenum and the upper part of the small intestine, and the important factors predisposing to iron deficiency appear to be the by-passing of the duodenum, the hurry of the meal through the jejunum, and the irritation of the small intestine which sometimes leads to steatorrhœa. However, although operations on the stomach interfere with the absorption of iron, hypochromic anæmia of any severity is unlikely to develop unless the factor of blood loss is also introduced.

Simple resection of the small intestine does not usually lead to megaloblastic anæmia nor does it lead to vitamin deficiencies or œdema. If the resection is extensive—more than half—it leads to diarrhœa, steatorrhœa and wasting; the patient starves to death. The condition has been called enteroprival sprue but I think the term small-gut insufficiency (Jackson *et al.*, 1951) is better. More commonly anæmia and malnutrition develop as a result of mechanical disturbances of the small intestine such as intestinal stenosis, intestinal anastomosis and gastro-colic fistula (Watson and Witts, 1952*a*). In these cases the ill-effects are attributed to stagnation in the small intestine or to fouling of the stomach and intestine by fæculent material. The abnormal bacterial flora appears to be important though the mechanism whereby it creates anæmia and malnutrition is obscure. It may be by provoking gastro-enteritis, with depression of the function of the mucosæ by inflammation or by mechanical blockage by mucus. This will give rise to deficiency of vitamin B_{12} if the stomach is involved and to deficiency of folic acid, possibly combined with deficiency of vitamin B_{12}, if the small intestine is involved. A second possibility is bacterial competition with the host. It is now believed that the fish tapeworm (*Diphyllobothrium latum*) produces pernicious anæmia in man by abstracting vitamin B_{12} from the small intestine and denying it to the host. It is possible that bacteria may do the same when there is fouling of the upper part of the small intestine. A further possibility is suppression of bacteria which produce vitamins and encouragement of bacteria which produce toxins which are antagonistic to the vitamins.

The "stenosis, anastomosis or loop syndrome" is characterized by macrocytic anæmia, hypoproteinæmic œdema and steatorrhœa. There is a suggestion that steatorrhœa is more severe with high loops and anæmia with low loops. Estimation of the vitamin B_{12} of the plasma and the results of therapy indicate that the anæmia is usually due to deficiency of vitamin B_{12} (Mollin and Ross, 1954). It is therefore not surprising that subacute combined degeneration occasionally occurs. This is a difference from sprue and idiopathic steatorrhœa, in which the anæmia is usually due to deficiency of folic acid and subacute combined degeneration is uncommon. It is also a difference from the similar syndrome which develops in the rat after the production of a cul-de-sac in the small intestine, as this is relieved by folic acid or by intestinal antiseptics but not by vitamin B_{12} (Watson and Witts, 1952*a*, *b*).

The mechanism of the deficiency of vitamin B_{12} is not clear. In several patients who responded to vitamin B_{12} parenterally it has been shown that the gastric juice contained free hydrochloric acid and intrinsic factor, or that the gastric mucosa was histologically normal. It seems, therefore, to be a disturbance in the absorption of vitamin B_{12} from the intestine, and the anæmia may improve as a result of the administration of intestinal antiseptics such as the antibiotics. Finally, there are a number of cases in which the anæmia has been permanently cured by restoration of the normal continuity of the intestine. Four hitherto unpublished cases of ours include two of megaloblastic anæmia after right hemicolectomy and anastomosis of ileum to colon, one of megaloblastic anæmia after multiple operations for intestinal obstruction and strangulation, and one of megaloblastic anæmia and loop syndrome after an operation to by-pass an intussusception.

In gastro-colic fistula steatorrhœa, wasting and hypoproteinæmic œdema are usually more prominent than anæmia. In one of our patients we were able to carry out a fat balance before and after an ascending colostomy which diverted the fæcal stream from the fistula. Before colostomy about 50% of the fat ingested was excreted in the stools whereas three months after colostomy only 7% was excreted.

REFERENCES

CALLENDER, S., TURNBULL, A., and WAKISAKA, G. (1954) *Clin. Sci.*, **13**, 221.

JACKSON, W. P. U., LINDER, G. C., and BERMAN, S. (1951) *S. Afr. J. clin. Sci.*, **2**, 70, 205.

MOLLIN, D. L., and ROSS, G. I. M. (1954) *Proc. R. Soc. Med.*, **47**, 428.

RAISH, J., and CAPPER, W. M. (1953) *Lancet*, ii, 597.

RIEMINE, W. H., and PRIESTLEY, J. T. (1952) *Surg. Gynec. Obstet.*, **94**, 519.

WATSON, G. M., and WITTS, L. J. (1952*a*) *Brit. med. J.*, i, 13.

——, —— (1952*b*) *J. Path. Bact.*, **64**, 232.

WELLS, C., and MACPHEE, I. W. (1954) *Brit. med. J.*, ii, 1128.

Professor Ian Aird:

The classification which Mr. John Bruce has arrived at for our guidance in discussion is to my mind a very suitable one. I do not wish to cover this field in full; I shall limit myself to a few rather disconnected observations on isolated aspects of some of the subjects to which Mr. Bruce has referred.

Paralytic (*adynamic*) *ileus* in the absence of peritonitis is a very rare phenomenon and I believe that it is seldom serious, now that gastro-intestinal suction drainage is available for the treatment of post-operative distension. Peristalsis is always recovered after a week at most, provided the intestine is kept sufficiently empty for its muscle to act at a suitable mechanical advantage. The situation in *toxic* (*peritonitic*) *ileus* is a more complicated one and my conception of the disease has some bearing on its treatment. After anæsthesia or operation peristalsis is inhibited for six to twenty-four hours, recovering gradually. This period of quiescence is greatly prolonged if the proteins have been low at the time of operation and if the electrolytes are low also. Potassium lack, perhaps related to normal post-operative adreno-cortical activity, may also be important (Streeten and Ward-McQuaid, 1952), and it may be prolonged if hexamethonium has been used (Mackey and Shaw, 1951). When the initially weak propulsive force of peristalsis returns, it may fail to overcome the impediment of the slender fibrinous adhesions which are present in peritonitis but which would be no obstacle to the powerful peristalsis of normal bowel. The recovering peristalsis seems almost to be discouraged and certainly to tire after its initial efforts, there is a pause of abdominal silence for some hours, and the peristaltic attempts are repeated. If they fail after several successive episodes of effort, the adhesions produced by the peritonitis may be sufficiently organized and the bowel sufficiently distorted by them to have the effect of organic obstruction. In this variety of obstruction, a neurogenic factor is acting in association with a mechanical factor. Gastro-intestinal suction can meantime keep the intestine empty, and adequate intravenous saline and blood plasma will encourage peristalsis, but it is sometimes found, admittedly exceptionally, that when gastro-intestinal suction is stopped, the bowel still fails to regain its propulsive function, and in my view this is then due to a mechanical factor. I have known some patients go on for as long as four or five weeks, and many patients who have gone on for as long as two or three weeks, having their gastro-intestinal suction interrupted and reapplied at intervals of a day or two. These patients are difficult to maintain in an adequate state of nutrition by intravenous therapy over so long a period, and their convalescence can be shortened and their health improved dramatically by the establishment, reasonably early, of a jejuno-transverse colostomy. A small para-umbilical incision is made and the first escaping loop of distended bowel is united by a small anastomosis to the transverse colon.

Immediately after the operation the abdominal distension seems to lessen, largely from a redistribution of gas to the colon, even though flatus is not usually passed for twenty-four hours. I have performed this operation on about two dozen patients who in the last twelve years have suffered from persistent and continuing peritonitic ileus and the results have always been gratifying. In most cases the by-passed small intestine seems to reopen and in these there are no nutritional disturbances. In one patient, a boy of 12, diarrhœa persisted after the anastomosis which had to be undone; within a few weeks he obstructed again and the anastomosis had to be refashioned; again there was trouble with diarrhœa, but the outbreak of war and my mobilization transferred this rather difficult problem to one of my colleagues. One other patient developed a macrocytic anæmia which was cured by the undoing of the anastomosis. I now perform jejuno-transverse colostomy about the tenth day after operation in a case of peritonitis if the intestine has not regained by then its propulsive function.

Post-gastrectomy œdema of the jejunum.—Two observations related to post-gastrectomy mucosal œdema may be of interest. After gastrectomy, and particularly after gastrectomy performed for the relief of pyloric stenosis, when the patient's serum proteins are often low and their electrolytes deficient, sometimes the total fluid intake by mouth is recovered by gastric suction, none of it passing from stomach to jejunum. This is often ascribed to œdema of the mucosa at the stoma, chiefly because, in a few cases, gastroscopy has been performed and an œdematous stoma brought to view. In 2 of our patients obstruction at the stoma has persisted for so long that we have suspected a serious mechanical fault and have re-explored on the tenth or fourteenth day. In both these patients a palpable œdema of the jejunal wall was present extending along many feet of jejunum. When an attempt was made towards the lower end of the œdematous segment to introduce a jejunostomy tube for feeding, it was found that the lumen had been so narrowed by œdema that it would not accept even the narrowest suitable catheter. Our conception of this post-operative syndrome has therefore changed, and we now believe it to be due to an extensive œdema, not of the stoma, but of a substantial length of the jejunum. In 2 subsequent patients we have been

forced to continue to remove by suction the whole oral intake of the patient for a period of three weeks in one case, and four weeks in another, both patients then recovering a patent jejunal passage.

REFERENCES

MACKEY, W. A., and SHAW, G. B. (1951) *Brit. med. J.*, i, 1205.
STREETEN, D. H. P., and WARD-MCQUAID, J. N. (1952) *Brit. med. J.*, ii, 587.

Mr. M. R. Ewing:

We have recently made attempts to reproduce in the experimental animal the megaloblastic anæmia which is well recognized as an infrequent but none the less important complication of operations on the stomach and small intestine. Following the same technique which was used successfully by Watson and Witts (1952) in rats, we failed completely to induce anæmia in rabbits, some of which were followed for as long as a year.

Dr. Selwyn Baker and I next tried to reproduce the results reported by German workers (Tönnis *et al.*, 1932) in the early 'thirties. They found that the creation of culs-de-sac in the small intestine of dogs led to the development of a high colour index anæmia which was relieved by liver therapy. Although the experiment is still going on, our results to date have been, in the main, disappointing for we have, in no single instance, succeeded in inducing a megaloblastic anæmia.

It is proposed to continue with this work, modifying both the operative procedure and the diet.

REFERENCES

TÖNNIS, W., HORSTER, H., REIMERS, C., and RÜDEL, C. (1932) *Z. ges. exp. Med.*, **84**, 782.
WATSON, G. M., and WITTS, L. J. (1952) *Brit. med. J.*, i, 13.

Professor C. G. Rob:

With reference to Mr. John Bruce's remarks on necrotizing enteritis, we have seen 6 such patients at St. Mary's, 3 after abdominal operations and 3 after other procedures; all had one or more of the recognized antibiotics in the immediate post-operative period. 5 recovered with the most energetic treatment. The huge fluid losses by diarrhœa and vomiting must be replaced; in one patient who recovered these exceeded 19 litres in twenty-four hours and this amount of fluid and associated substances was given intravenously over the same period. In all our patients a penicillin-resistant staphylococcus has been present in the gastric aspirate; this infection, which we believe causes the necrotizing enteritis, has been treated by very large doses of penicillin given down the gastric aspiration tube. By this means a high concentration of penicillin was attained locally in the stomach, sufficient to destroy the penicillin-resistant staphylococcus.

Mr. D. C. Corry discussed Professor Charles Rob's statement that in 6 cases of necrotizing enteritis following partial gastrectomy he had been able to culture *Staphylococcus aureus* from the gastric aspiration.

Mr. Corry went on to say: I noticed these cases were liable to be multiple in wards and so considered they were infective in origin. Infection appeared to start when milk feeds were given and to occur in a ward where there had been another case of diarrhœa, not necessarily, but usually, a gastric operation.

Cases occurring on the third and fourth day were the ones which caused the mortality. Diarrhœa occurring for the first time on the fifth or sixth day was milder and not likely to be fatal.

Staphylococcus aureus has been grown in one case from the stool but only following a request that this should be looked for specifically, as in the normal examination of the stool for pathogens staphylococcus was not looked for.

Eighteen months ago I reverted to the old practice of gastric feeds being given as a sterile feed. The milk, sufficient for 4 to 6 feeds only, was boiled and kept specifically for that patient. Until we know infection is not the cause it is certainly wise to give sterile feeds.

The diarrhœa often starts at night so that it is necessary to have a drill to ensure that large quantities of intestinal replacement fluid plus big doses of antibiotic by mouth are given before the patient gets dehydrated.

Not every case which came to post-mortem showed the pathological changes of necrosis in the intestinal mucosa.

Mr. N. C. Tanner:

Severe nutritional disturbances may follow chronic obstruction of the small intestine. In 1936 I reported before the Clinical Section of this Society a case of infantilism occurring in a young man as a result of chronic ileal obstruction due to Crohn's disease (Tanner, N. C., 1939, *Proc. R. Soc. Med.*, **32,** 34). This patient gained height and weight considerably after the obstruction was relieved surgically.

I was interested to hear of the remarks on the long latent interval which may occur after gastrectomy before anæmia may develop. In a review of a group of cases of partial gastrectomy carried out at St. James's and the West London Hospitals, my friend Mr. Harold Burge found that there was a tendency for the average hæmoglobin percentage to diminish a little each year. For example, of the male cases only 1 out of 50 cases had a hæmoglobin below 75% at the end of the first year after gastrectomy. At the end of the fourth year, 14%, and at the end of the sixth year, 24% had a hæmoglobin under 75% (Tanner, N. C., 1954, *Trans. med. Soc. Lond.*, **70,** 171). A similar delay may occur before megaloblastic anæmia occurs after total gastrectomy. 2 of my longest surviving total gastrectomies for carcinoma reached the fifth and sixth years after operation without any appreciable anæmia and yet just after the seventh year both developed a pernicious type of anæmia. Both have been corrected by the appropriate treatment. Retention of even the minimum of stomach may delay the onset of anæmia. Two other quasi-total gastrectomies, that is not quite total resections (one of them having 1 cm. of the cardiac end and the other 3 cm. of the pyloric end retained) have remained without a megaloblastic anæmia although both have gone well over ten years since operation.

Dr. W. A. Bourne:

The only comment I can make at the moment is to support Professor Witts' statement about atrophic changes in the gastric mucosa after gastrectomy. I have recently reviewed my cases gastroscopically examined, and of those referred to me because of symptoms following gastrectomy I estimate about 8% have atrophic gastritis. I think this is sometimes associated with hæmatological and intestinal disturbance.

Section of Otology

President—JOSEPHINE COLLIER, F.R.C.S.

[*November* 5, 1954]

The Art of Otology

PRESIDENT'S ADDRESS

By JOSEPHINE COLLIER, F.R.C.S.

"A practical art has no complete and sure foundation of ascertained principles. Its possessions are made up of separate and fragmentary conquests from the unknown."
Collected Papers of Wilfred Trotter.

ABSTRACT

Management of chronic ear infections dependent on recognition of the differences (pathological and clinical) between tympano-tubal lesions and attico-antral disease. Chronic suppurative otitis media as a reason for rejection for military service. Statistics obtained from the Ministry of Labour and National Service. Relative incidence of tympanic and attico-antral disease in a series of 500 hospital patients at the present time. Resistant chronic tympanic disease still a problem. Relation to acute suppurative otitis media. Recurrent and relapsing attacks of acute otitis media. Does early chemotherapy interfere with development of immunity?

Problems presented by acute otitis media likely to be elucidated by the general practitioner rather than by the otologist. The general practitioner's opportunities for research in this clinical problem. Incidence of ear diseases in average general practice.

Training of medical students in diseases of the ear, nose and throat. Methods of instruction followed in the teaching schools of Great Britain and Northern Ireland and attitude of the Examining Bodies to this subject. The contribution of otologists to the education of doctors.

Some observations on facial paralysis. Importance of prognosis. Different criteria in early and late stages of paralysis. Reasons for abandoning the faradic-galvanic tests in the management of facial paralysis. Use of constant current square pulse stimulators in early days of facial paralysis. Electromyography of value in later stages.

Present-day difficulties in acquiring skill for facial nerve surgery. Importance of the stylomastoid artery. Recent investigations on the blood supply of the facial nerve: gross vascular pattern and the interfascicular plexus. Further work necessary to relate these anatomical facts to the condition of Bell's palsy.

PRESENT-DAY VIEWS ON THE MANAGEMENT OF CHRONIC EAR INFECTIONS

THE changing pattern of practice in the management of middle-ear infections during the past quarter-century derives equally from the introduction of chemotherapy and antibiotics, and the recognition in chronic otitis media of the differences (pathological and clinical) between tympano-tubal lesions and attico-antral disease. No otologist nowadays subjects the pure tympano-tubal lesions to operative treatment, frequently done in the past with deplorable results. Better appreciation of the varied pathology responsible for chronic otitis media has taught us that only when we find attic or antral disease should operations be considered. This more precise selection has been accompanied by a more flexible attitude to the actual operation and the evolution of forms of modified radical proceedings of the epitympanic type with emphasis on conservation of hearing. The dual aim of safety and conservation of hearing should require from us a rigorous assessment of each patient. We have as yet no complete body of established principles regarding the nature of the pathological processes which affect mucous membrane closely adherent to bone in the confined space of the middle-ear cleft. Our treatment of an individual case derives more from experience than from applied principles and by experience I mean that feeling for his material which the follower of a practical art must possess. As attempts to extend the frontier beyond the region of art towards the more exact and definable field of applied science I would point, first, to McCuckin's paper (1953) on the management of chronic otitis media with the emphasis on accessibility of the lesion, irreversible pathology and nutritional defects in mucosa and

adjacent bone, and second, to Thorburn's (1954) clinical classification for designing operative treatment. Even here we are concerned, not with a rigid technique, but with the right management of our material—material which is never inert but an active element in our art. The importance of preserving as much as possible of the tympanic membrane is shown by the better hearing obtained when a mobile membrane is achieved.

Chronic Ear Infections as a Reason for Rejection from Military Service

Recognize now the achievements of chemotherapy and antibiotics; better control of acute infections of the ear still leaves the otologist with his problems. Let us see what is the incidence of chronic ear disease at the present time. Johnston's (1948) survey in Birmingham showed that 3·3% of 1,900 factory workers selected at random, i.e. making no complaints of ear symptoms, had active middle-ear disease. The bulk of the specialist otologist's work in the Army during the last war was concerned with chronic otorrhœa and even at that time there was a high rejection rate for ear diseases. A study of the records of the Ministry of Labour and National Service Medical Boards which Formby (1945) made during that war showed that diseases of the ear were responsible for 10·6% of the total number of men rejected from all causes. I thought, therefore, it might be enlightening to know the present rejection rates for these diseases.

Through the courtesy of the Ministry of Labour and National Service, I have learnt that no detailed analysis is kept of the reasons for rejection of National Service men on medical grounds, but in 1950 and again early this year a review was undertaken of the causes which led to men being placed in low medical categories, and an analysis was made by the Regional Medical Officers of a cross section of medical reports relating to men placed in Grade IV, that is, the men who are not called up for National Service. The first analysis was for six months in 1950 and covered 5,000 men. The 1954 analysis for the period of six months ending March 31 related to 7,000 men. The reasons for rejection which concern the otologist are three, ears other than radical mastoids, radical mastoids, and hearing. Table I shows ear disease above 20%, and at the head of the list of all the conditions which make a young man unfit to serve in the Armed Forces.

Table I.—Rejections for Military Service: Grade IV

	1950: 5,000 men	1954: 7,000 men
Ear (other than radical mastoid)	20·7%	19·1%
Radical mastoid	1·6%	1·6%
Hearing	1·3%	0·9%
No other disability produced over	20·7%	19·1%

There were discussions on the effect of middle-ear disease and fitness for active service at joint meetings of the Section of Otology and the United Services Section in 1928 (*Proceedings*, **21**, 1455) and in 1937 (*Proceedings*, **30**, 1523). At the 1928 meeting it was stated that 7% of the total rejections of recruits for the R.A.F. during the previous five years were for aural disease; even so far back as the 1920s the R.A.F. was in a position to demand a rigorous standard of aural fitness so these rates are comparable with the present figures.

Table II.—Rejection Rates for Ear Diseases

R.A.F. 1922–1927	7·0%
Ministry of Labour and National Service (1939–1941) ..	10·6%
" " " " 1950	20·7%
" " " " 1954	19·1%

Even allowing that aural examination is more thorough to-day study of Table II should be salutary. We are challenged by the fact that nearly twenty years after the introduction of chemotherapy, service rejections on account of ear disease of young men born in 1936, are around 20% of the whole—the highest single cause for exclusion.

These rejections for chronic ear conditions will presumably include all types of middle-ear disease, ranging from the pure tubal recurrent case with intermittent mucoid discharge to attic disease and cholesteatoma. Would a better classification by otologists, based on our recognition of the natural history of these varied types, have an appreciable effect on the man-power problem by allowing recruitment of those with tympanic lesions? Apart from the fact that every middle ear with an open perforation and exposed mucosa is easily liable to exacerbation or reinfection with upper respiratory infection, after bathing or in tropical countries, the man with an ear discharge has a ready excuse to "go sick" when he wants to avoid uncongenial duties. Unless unit medical officers are familiar with the significance of the tympanic appearance, the conjunction of ear discharge with a complaint of headache or "black-outs" will lead to much wastage and absence from duty.

Chronic Tympanic Infections

Chronic otitis media with disease confined to the mucosa of the middle ear and eustachian tube, with or without polypi, form the bulk of so-called "cures", i.e. temporary cessation of discharge, in the various series of trial of conservative treatment which have been published in recent years (Johnston, 1948; Lewis and Gray, 1951; Rutter and Ballantyne, 1952).

Each new antibiotic has its trial. Lewis and Gray's careful paper on the topical use of chloramphenicol claimed only results as good as those produced by any other method with less expenditure of time and trouble. It is interesting to note that Rutter and Ballantyne, using penicillin, streptomycin, chloramphenicol and Terramycin, obtained their best results with Terramycin, the latest antibiotic available. They found no constant relation between the sensitivity of the organisms and the clinical response to the antibiotic employed, and suggest that this inconsistency may have been due to changing flora. This is my own experience and I believe there is too great an emphasis on bacteriology in the management of chronic ear infections. This applies even more forcibly in external otitis where constitutional factors, a seborrhœic quality of the skin, the psychological make-up of the patient and his habits, influence the outcome of treatment far more than the temporary microbic inhabitants. In both middle and external ear disease acute skin sensitization of the outer ear is nowadays too lightly and too easily induced.

Relative Incidence of Tympanic and Attico-antral Disease

What is the relative incidence of "safe" and "dangerous" chronic middle ear disease at the present time? Török (1937) analysed 500 consecutive cases of chronic otitis media and found central perforations in 182 and marginal in 318. My figures have been obtained from examinations of 500 out-patient notes, collected from the Royal National Throat, Nose and Ear Hospital for which I am indebted to the surgeons concerned, and from my own out-patients. In every case the patient had attended complaining of a long-standing discharging ear. The classification has been simple: central perforations of the membrana tensa not involving the tympanic margin are called tympanic; postero-marginal, postero-superior and attic perforations are called attico-antral. The figures are 165 central tympanic perforations and 335 marginal attic perforations. I have entered them on Table III as the 1952–1953 group.

Table III.—500 Cases of Chronic Suppurative Otitis Media

	Tympanic (central perforations)	Attico-antral (attic or marginal perforations)
Török (1937) ..	182	318
1952–1953	165	335

Even if our experience tells us the incidence is decreasing these cases still form a considerable problem. The best we can hope for with the best management is cessation of otorrhœa or a dry ear, always vulnerable. Neglected, and in the less intelligent and unskilled sections of the population neglect is inevitable, the ear can become foul from stagnation of the discharge in the meatus and mixed infections. Perhaps I get a prejudiced view from the district in London where my main hospital is situated but it seems there are too many kitchen workers with active ear disease. I sometimes wonder if the teachers of social medicine when they organize trips with their students to the food manufactories realize this aspect of employment. Should we say it has fastidious importance, as well as one of hygiene?

I need not stress the disability of progressive deafness which accompanies resolution of chronic middle-ear infections when repair can take place only by fibrosis in the mucosa leading to adhesion around the ossicles and windows. Johnston (1948) showed that out of 393 cases of severe deafness 49·3% were due to active or healed otitis media. I have looked through a consecutive series of patients whom I have sent for hearing aids to see how many have a history of long-standing otorrhœa in the past and/or evidence of the tympanic membrane of healed perforations. In the last 100 patients requiring an aid to hearing I find 47 showed evidence of past or present otitis media, a percentage near to Johnston's.

The common observation that some patients with intermittent ear discharge hear better when the ear is moist is compatible with the experience that continued activity leads to deterioration of hearing, whether healing occurs or not. Proper management of middle-ear disease in the early stages before irreversible changes take place is therefore desirable if preventable deafness is indeed to be prevented.

Is Chronic Tympanic Disease a Sequel of Acute Suppuration?

Must we regard these cases of chronic, i.e. resistant, tympanic disease inevitable? I take it for granted that any nasopharyngeal sepsis will be corrected but it will be everyone's experience that this only occasionally leads to healing.

We know that defective pneumatization is sometimes present in tympanic as well as in attic disease and cholesteatoma. I am sure, however, that the size of the cell system should not be given undue weight. I believe myself—and strongly—in opposition to those theories which give all the blame to the architectural quality of the mastoid bone—that chronic tympanic disease dates in most cases from an attack of acute otitis media. The widespread association of persisting infection with poor social conditions surely suggests that dirt and neglect, favouring contamination and mixed infection, play a part. This is perhaps an old-fashioned view and it may be that hygienic factors have effect only in the early months of life. Neglected upper respiratory infections may lead to alteration in the mucosa of the middle-ear tract, making it more vulnerable to later infections as well as interfering with cellular development. Theories of pneumatization are outside the scope of my Address. I need only refer to the challenge now offered to the views of Dahlberg and Diamant (1945) by Tumarkin (1953) and by Ojala (1950). In this connexion an analysis of the radiological appearance of 218 cases of cholesteatoma (proved at operation) in the series of 500 patients with chronic ear discharge gives material for speculation (Table IV), raising doubts as to whether even in cholesteatoma an inherited pattern of pneumatization is the chief factor in ætiology.

Table IV.—Radiological Appearances in 218 Cases of Cholesteatoma

Both side acellular (sclerotic and diploetic)	98
Both sides cellular (cells cloudy on affected side)	33
Mixed: partly diploetic, partly cellular (cells cloudy on affected side)	3
Affected side sclerotic. Sound side cellular	84
	218

We may find an acceptable explanation for chronic tympanic infections by considering the pathological and bacteriological findings encountered in those cortical mastoid operations we perform nowadays for acute suppurative otitis media that has failed to resolve with antibiotics—probably the main indication for a simple mastoidectomy at the present time. Frank pus is seldom present and if such be found it is likely to be sterile or to grow Gram-negative organisms. We commonly find the antrum and aditus, and the mastoid cells filled with swollen mucosa, sometimes œdematous but more often hyperplastic. It is interesting to speculate on what would have happened if no operation had been performed. Not all, perhaps very few, would go on to a mastoid abscess; the mucosa in the antrum could fibrose while discharge from the middle ear persisted and chronic otorrhœa be thereby established. Alternatively the exudate may become organized and chronic adhesive processes lead to deafness.

Friedmann's experimental work (1954) gives some support to these observations. He found in the guinea-pig that chronic otitis media followed directly on acute suppurative otitis media, sometimes developing in an insidious way after an initial latent period; at other times with new bone formation leading to thickening and bony obliteration of the cavities of the middle ear. In the guinea-pig new bone formation occurs characteristically with the Gram-negative organisms while streptococcal infections were on the whole milder. The lining of the middle ear cavity and pneumatic cells, normally of flattened endothelial type, becomes changed into tall, columnar, ciliated, epithelium with many goblet cells—changes similar to those seen in the human middle ear with chronic tympanic infection.

Present-day Problems of Acute Otitis Media

Acute otitis media can present other problems besides the danger of lapsing into chronicity. I have recently analysed a series of 120 consecutive cases in children under 12 years of age seen at one hospital in 1951 and 1952. All had adequate chemotherapy or penicillin and the usual modern management both of the attack and of the nasopharynx. Only 6 required myringotomy. Of this 120, 75 had had no previous ear disease; the tympanic membrane healed satisfactorily and hearing was restored in those old enough to be tested. There has been no recurrence in these 75.

34 either had a history of previous recurrent attacks or had repeated attacks later. Treatment for the previous attacks and management of the nasopharynx, so far as could be judged,

had been adequate. I have labelled 11 of the 120 as relapsing when the infection appeared to have cleared up after treatment but recurred within two months.

TABLE V.—ACUTE SUPPURATIVE OTITIS MEDIA
120 Consecutive Cases

First attack healed under treatment	75
Recurrent attacks	34
Relapses	11
	120

7 of the 120 required a simple mastoidectomy: 2 of the 75 with a first attack of otitis media, 3 with a history of recurrent attacks and 2 of the 11 relapsing cases.

This small series serves to confirm an impression that recurrent and relapsing attacks are still a problem, in spite of the satisfactory management of chronic nasopharyngeal disorders both in the child population at large and in individual patients with acute otitis media. We must all have wondered why some children seem to get a middle-ear infection with every cold even though their nasopharynx is healthy and there is neither persisting sinusitis nor nasal allergy. At the discussion on the management of acute otitis media which my predecessor in this Chair opened last summer at the meeting of the American College of Surgeons, he commented on the high incidence of repeated attacks among children of one's medical colleagues—an experience many of us must have had—and I wonder if we may find a clue here. These children are apt to be given sulphonamides, or, nowadays, oral penicillin at the first sign of earache or early injection of the tympanic membrane. Is it possible that the development of immunity is thereby impeded? This clinical aspect of immunity was discussed at the Section of Medicine in 1954 (*Proceedings*, **47**, 623) when bacteriologists commented on an interference by antibiotics with the natural course of disease thereby reducing the number of infecting organisms before they can provide sufficient stimulus to the production of antibodies. In this connexion Dr. Nuala Crowley reminds me that immunity to infection by hæmolytic streptococci, for example, is both antitoxic and antibacterial. Whilst antitoxic immunity is against Group A streptococci in general, antibacterial immunity is type-specific, and does not protect against reinfection by a different type of Group A streptococcus. The existence of another type of antibacterial immunity which is not type-specific has by no means been ruled out. Both penicillin and sulphonamides may rapidly suppress the toxic symptoms of infection, but non-type-specific resistance may not have time to develop. But here I am straying beyond my theme and my capacity. We cannot withhold antibiotics lightly nor can we recommend others so to do unless we have taught them to assess by observation the significance of otoscopic changes.

ROLE OF THE GENERAL PRACTITIONER IN MANAGEMENT OF EAR INFECTIONS

The management of acute ear infections in this country, and rightly so in my opinion, is largely in the hands of the general practitioner. The family doctor should, moreover, hold first place in the care of children in their infant years; that is, in the period when morbidity from upper respiratory infections is at its height. The Newcastle survey (Spence *et al.*, 1954) into the health and sickness of a thousand children revealed the immense significance of infectious disease. Of these thousand infants only 20% escaped illness during the first year of their lives, while 86% of all illnesses were infective in origin—upper respiratory infections, bronchitis, pneumonia and gastro-enteritis. We, as otologists, are concerned to know how chronic ear infections—both tympanic and cholesteatomatous—are caused. It may well be that the conditions predisposing to chronic ear disease occur in the early months of life as was suggested earlier. If this be so it will be the general practitioners rather than ourselves who will throw light on the problem of ætiology. The family doctor alone is in a position to observe the natural history of ear infections, especially in epidemics of acute upper respiratory infection. We need the observations of the general practitioner to add to the corpus of our knowledge. How often and under what conditions does acute otitis media become chronic? Why does a central perforation persist in one case after acute otitis and heal in another even though in both infection has cleared? Most important, will it be possible for early attic disease to be revealed before cholesteatoma has done its damage?

Lest it may seem that I am asking too much from overburdened practitioners I can refer to the first Annual Report of the College of General Practitioners (1953) where welcome is given to the White Paper on Clinical Research in Relation to the National Health Service. Here is a challenge to the general practitioner who sees the onset of disease to contribute to the general study by recording his observations. The Research Advisory Panel of Consultant Experts was established to encourage accurate observation by general practitioners

and to co-ordinate and record the results. The value to medical research will be obvious. The Research Panel has even suggested methods of collection of material, designed to throw as little strain as possible on the daily routine work, and the report mentions cards and flimsies suitable for such investigations, which would fit into the National Health Service envelopes.

If it appears that I have wandered far from the title of my Address I have failed in my purpose, for I hold that the art of otology is practised by the general practitioner no less than by ourselves. A soundly cultivated judgment depending on familiarity with the material of the art, i.e. experience—not merely the aptitude of the craftsman—is necessary in the management of ear disease at every level, and progress in knowledge on the lines I have indicated is likely to come mainly from the exact observations of informed practitioners.

How far does medical education at the present time provide the basis for the general practitioner's responsibilities in this respect?

At a meeting of the Section of Laryngology in 1951 on The Role of the General Practitioner in Otolaryngology (*Proceedings*, **45**, 158) many of those present expressed dissatisfaction with the teaching they had received as students, while stressing the large number of ear and throat cases which occur in general practice. Attention was drawn to the major difficulty of making an accurate diagnosis with inadequate diagnostic equipment though it is recognized nowadays that the general practitioner must be a specialist in diagnosis. I thought, therefore, it would be useful to know what proportion of the family doctor's work is concerned with otology. At the meeting just referred to it was agreed by the general practitioners that over one-third of all cases required some form of ear and throat examination. I had thought that they must have been referring mainly to acute infections of the pharynx and the common cold and I have been surprised to learn how much of the general practitioner's time is taken up with ear diseases as such. The morbidity report which the General Register Office (1954) has brought out based on an analysis of the clinical records of eight practices of varied types (during the period April 1952 to March 1953) shows that otitis media takes fifth place in the table of principal diseases and conditions diagnosed.

Training of Medical Students in Ear, Nose and Throat Diseases

Now a practical art must be judged by what it can do. How do we fulfil our function as teachers—teachers to undergraduates and to our colleagues the general practitioners? On the assumption that an enquiry into the methods of teaching medical students might be pertinent to a discussion on the management of ear infections in general practice, I have sent a questionnaire to the senior ear, nose and throat surgeon in each teaching hospital in the country. I am indebted for their reports which inform this part of my Address.

At all save one medical school in London, attendance at the ear, nose and throat out-patient department is a compulsory part of the medical course, although compulsion is interpreted widely in the adult British way. In most medical schools attendance is required at one to three out-patient sessions per week for two to three months. During this period the students also attend one or more other departments—the old grouping of "specials". In Newcastle, however, the students are attached to the ear and throat department exclusively for one month. Aberdeen requires two weeks' full-time attendance in 10 daily consecutive sessions. A separate clinical teaching room adjacent to the out-patients department is available and after learning how to examine each other, the students are attached to the ear, nose and throat department in groups of less than 10. Selected patients are examined in the teaching room under the supervision of one of the consultants, who undertake this duty in turn, while the routine work of the out-patient department is carried out by the others. This intensive two weeks' course is found to be too short as students are only starting to acquire facility with their tools and a beginning of confidence when the time is ended. I was interested to learn that Mr. Simson Hall believes from his experience of short extra-vacation courses held in Edinburgh during the war, that students would be taught better in small groups, say 6 to 10, attending the department whole time for three to four weeks rather than the present system of a longer period of divided attention, when other subjects are studied at the same time.

As regards the methods of examination it appears that use of the head mirror is taught in all schools except at Leeds where Mr. G. S. Seed advocates the use of headlamp and auriscope alone. Although many teachers believe that the majority of general practitioners would find a headlamp and an auriscope more convenient and that very few use a head mirror in practice, several senior surgeons declared that proper training can only be given with a head mirror. From Oxford we learn that the head mirror is encouraged as being a valuable skill for all and Mr. R. G. Macbeth recalls how it can be used with a candle in a cottage. On the other hand, Mr. H. V. Forster recommends the headlamp very strongly, pointing out that it can also be used when repairing a torn perineum in a country cottage.

If he were allowed to dictate he would make compulsory absolute efficiency with the headlamp.

As regards questions in the final qualifying examinations the Provinces, Scotland and Northern Ireland give more attention to otolaryngological subjects than do London University and the Conjoint Board. These two examining bodies only occasionally have a question on some aspect of ear, nose and throat work and never a clinical or *viva voce* examination conducted by otolaryngologists, despite the belief of all the teachers that the expectation of such questions would lead to better training of the future doctor. Most universities in the country always have such a question—some a compulsory one. At Sheffield the otolaryngological question is answered in a separate book and marked by the lecturer in otolaryngology and there is also a *viva voce* examination. At Cardiff there is nearly always a relevant question in the final examination but the ear, nose and throat surgeons are not examiners. Some universities have a clinical examination and *viva voce*, e.g. Oxford, Liverpool, Manchester, Bristol; perhaps as an alternative with ophthalmology or anæsthetics; the candidate not knowing which subject he will get until the day of the examination. In these examinations the ear and throat surgeons take part. At Liverpool the senior otolaryngologist forms a team with two general surgeons. He presents alternative questions to the Board of Examiners and marks the answers. At Oxford since the *viva* was introduced it has become easy to judge which London schools take their ear and throat teaching seriously.

At all the clinical and *viva voce* examinations attention is devoted mainly to methods of examination and the diagnosis of simple cases, such as perforations of the tympanic membrane and the presence of polypi.

Edinburgh, true to its tradition of sound basic theoretical training, has a paper of four questions and, perhaps, an oral. A candidate failing to reach 50% has to take the examination again or even both clinical course and examination. Only St. Andrews follows the recommendation of the Goodenough Committee and has a departmental class examination. Those not satisfactory must report for further clinical work.

It was obvious from the various reports that emphasis in teaching was on clinical observation and not on specialist techniques, the aim being to give the student the opportunity of distinguishing the abnormal from the normal. More than one surgeon suggested that if this skill is achieved the student has acquired an art that most general practitioners who refer cases to the hospital still lack. Otologists are not unmindful of the weight of the curriculum and when they consider more attention should be given to ear and throat work, their thought is not of dealing with the problem by accretion, but rather, of making better use of the time available and a more rational integration into the medical course. Some hospitals include practical instruction in methods of examination on fellow students in the introductory clinical course. Students thus learn early to associate otolaryngological symptoms with general medicine. A wrong emphasis appears in one teaching hospital in the North where ear, nose and throat work is no longer practised or taught in the general teaching hospitals but is now concentrated in a special hospital. It is felt that this reorganization has probably done more harm to the residents and registrars in the general hospitals than to the undergraduate medical students but the segregation of subjects must limit experience for all.

The question is sometimes raised of the difficulty of giving adequate attention to students in the out-patient department. This problem may be met by selecting cases for examination in specially equipped students' teaching rooms. Not every ear and throat department has sufficient trained members of staff for segregated teaching and in any case it is important that students should see the routine work of the out-patient department—minor cases with common symptoms as well as patients with obvious clinical signs.

Can "General Principles" be Taught Through "Special" Subjects?

The problems of undergraduate medical education at the present time—and our particular responsibility for a special discipline—must be discussed in the light of the rapid changes taking place in medical practice. The great increase in knowledge and the complicated techniques employed in diagnosis in every branch of medicine make this a time of transition. It is recognized nowadays that the undergraduate training of a doctor is no longer concerned primarily with education for general practice but should be designed to lay the foundation for any form of medical practice. This is generally described as the teaching of general principles.

In his Presidential Address to the Section of Surgery on A Surgeon and Medical Education (1952) Mr. David Patey had some severe things to say on the confused thinking which attaches to this question. "It is often stated", he says, "that the student is too much stuffed with factual details and that his education should deal more with general principles. As a corollary the idea has grown up that there are certain departments of medicine and

surgery which teach general principles and not factual details (often identified as departments of general medicine and general surgery); and departments which teach specialized methods of observation and technique (often identified as special departments)." He goes on to examine these ideas critically and points out that . . ."fundamental principles are often delicate things to handle in the raw. And to get at them one may have to drive through a mass of factual details".

The second idea that there are two types of clinical department, general and special, with two totally different qualities and functions is, he believes, no longer tenable. "All knowledge is now necessarily in compartments, though the walls of the compartments should be elastic and movable and have wide inter-communicating doors". Mr. Patey sees certain consequences follow from these views. "The most important is that there is no reason why many of the special departments should not become general medical and surgical firms, i.e. firms which receive students as an integral part of their organization and demonstrate the general principles of medicine and surgery." I have not heard that these suggestions have been received with enthusiasm by the Deans of the medical schools. It might, however, be well to examine a little more closely the particular contribution which we as otologists can make to the education of doctors. I would put training in precise observation and exact description first; for this, familiarity in the handling of simple instruments—the acquiring of simple skills—is imperative. Then, there is the place which the taking of a concise and accurate history must play in our diagnoses—I need only mention the patient who arrives complaining of giddiness. Much consideration in the modern teaching of medicine is given to the interdependence of body and mind. Three common symptoms—deafness, vertigo and tinnitus—call for the understanding of physical and psychological mechanisms which demand a most searching interpretation on the part of the doctor. It is a common reproach to those practising specialties that they are apt to lose their perspective and not see the patient as a whole. The synoptic approach, however, has become as necessary for us, and as possible, as for the followers of other disciplines. Many conditions demanding our attention are not only local lesions but are expressions of various systemic disorders. I can speak here as an otolaryngologist and mention such diverse conditions as Ménière's disease, inner-ear deafness, external otitis, nasal allergy and nasal catarrh.

I would say that once a student has acquired a basic familiarity with our subject and a zest for fitting its problems into the pattern of disease he studies in other departments he has cultivated an aptitude which will enlarge every aspect of his work.

Prognosis in Facial Paralysis

I must now turn to the surgery of the facial nerve in relation to otology as an art. This involves first a consideration of the material—the nature of nerve pathology. Ramon y Cajal and his followers provided the scientific background that taught us the essential difference between the degenerative and the non-degenerative lesion, but in the practice of medicine there has often been difficulty in making this distinction. Nevertheless the patient's chief need at the onset of facial paralysis is for prognosis and, if possible, the comforting assurance that there will be recovery.

Prognosis is indubitably an exercise that calls for every faculty and every aid the doctor can command. Clear thinking is the primary requirement and that demands an understanding of the changing state of the nerve and the application of different criteria in early and late stages of paralysis. In the period immediately after onset the questions we must ask ourselves are these: Is degeneration impending? Or is the nerve in a state of reversible block to conduction which recovers without degeneration. My colleague, Dr. A. T. Richardson, has seen reversible block or neuropraxia persist in the facial nerve for as long as seven months. My longest case endured for three months. Electrodiagnostic aids provide this diagnosis but clinical proof depends on the high standard of recovery; there are none of the defects which accompany regeneration, i.e. associated movements, contractures and wasting.

After degeneration, recovery, whether spontaneous or as a result of operation, can take place only by regeneration. This progress naturally is slow in pace; whilst there is still paralysis, prognosis requires that we seek for evidence of impending regeneration.

The use of the techniques of electrodiagnosis in medicine may seem an example of the application of scientific methods in a practical art. Trotter (1941) in his Collected Papers reminds us "that the rule of science in medicine is still not more than strictly local and much qualified . . . Methods of precision", he says, "must be very strictly subject to the art of medicine if they are not to become a mere snare. The affectation of scientific exactitude in circumstances where it has no meaning is perhaps the fallacy of method to which medicine is now most exposed". I think the continued use of faradic-galvanic tests merits these strictures. It has long been known that the faradic response may be negative even when voluntary power is returning; moreover, a faradic response can, at times, be obtained

in a muscle known to be deprived of its nerve supply. A single examination is thus easily misleading while even in experienced hands these tests have a limited value, being essentially qualitative so that serial examinations are not comparable.

With deliberate intention I put forward the opinion that the time has come to abandon the faradic-galvanic reactions in the management of facial paralysis. I have hesitated to speak thus strongly before, because I myself have been fortunate in being associated with a department of physical medicine where the exact quantitative methods developed in physiological research—the use of intensity-duration curves and electromyography have been employed. The late Dr. A. J. Martin and now Dr. A. T. Richardson, as well as Professor Ruth Bowden of the Anatomy Department of the Royal Free Hospital, have in recent years provided me with the scientific background and the technical aids which have made possible any practical contribution I have been able to make to this subject. We cannot, however, expect such facilities to be general, nor the opportunities to acquire skill in interpreting them. But there are now available electrical stimulators which place nerve testing on a quantitative basis. These constant current square pulse stimulators have the great merit of being simple to use.

Diagnosis of Nerve Degeneration, Early and Late

Let us now consider a patient with facial paralysis of recent origin, without reference to the cause. This is a common problem. The technique used with the constant current stimulator is based on the fact that if a nerve is divided that portion of it remote from the motor nerve cell ceases to conduct impulses in a few hours. If a contraction of the muscles results when the facial nerve is stimulated (by 1 msec. current) at its exit from the stylomastoid foramen, any lesion proximal to the foramen is a non-degenerative one or at the worst there is only a minimal amount of degeneration. Alternatively if nerve conduction is absent, i.e. if stimulation of the nerve fails to bring a contraction we can presume that degeneration is occurring. If nerve conduction is present it is well to repeat the test on the third, fifth or twentieth day. After the fifteenth day more exact information, i.e. the degree of lower motor neurone degeneration or the degree of neuropraxia can be obtained only by more elaborate examination—plotting of intensity-duration curves by the same stimulator, and by electromyography. The particular value of electromyography is for detecting evidence of impending reinnervation when there is no clinical recovery. Signs of regeneration of the facial nerve may be obtained many weeks before movement can be seen.

Table VI shows how finding motor units at varied periods after the onset of paralysis told us reinnervation was occurring, i.e. that recovery would follow without interference.

Table VI.—Electromyography. Operation on Nerve not Indicated

Cause of facial paralysis	Duration without signs of recovery	E.M.G.	Clinical signs of recovery
Endaural mastoidectomy ..	10 weeks	M.U.s F.A.P.s	3 months later
Cortical mastoidectomy ..	20 weeks	M.U.s F.A.P.s	2 months later
Fractured skull	17 weeks	M.U.s F.A.P.s	2 months later
Penetrating injury	13 weeks	M.U.s A few F.A.P.s	1 month later
Herpes	23 weeks	M.U.s F.A.P.s	3 months later
Bell's palsy	12 weeks	M.U.s F.A.P.s	3 months later

M.U. = Motor Unit. F.A.P. = Fibrillation Action Potentials.

Table VII shows the value of electromyography in giving prognosis after operations on the nerve. It is not a strict follow-up as we were not always able to see these patients at regular periods. There may have been earlier evidence of motor unit potentials than appears in in the third column. The point of this table is that the motor units were present when there were no signs of clinical recovery. Similarly in the fourth column clinical signs of returning movement may have been earlier in some cases. It was present when we examined the patients at the periods after operation mentioned.

This information in contrast to that yielded by the faradic-galvanic test provides a guide to prognosis. Without such guide prognosis should remain dependent on clinical evidence.

TABLE VII.—ELECTROMYOGRAPHY AFTER OPERATION ON THE FACIAL NERVE

Cause of facial paralysis	Operation	Motor units but no clinical evidence	Signs of clinical recovery
Radical mastoidectomy..	Nerve graft	12 weeks	14 weeks later
Fenestration	Decompression	16 weeks	4 weeks later
Gunshot wound.. ..	Nerve graft	15 weeks	19 weeks later
Cortical mastoidectomy	Nerve graft	17 weeks	10 weeks later
Fractured skull	Decompression	24 weeks	8 weeks later

TRAINING IN SURGERY OF THE FACIAL NERVE

Seed (1950) and Simpson (1954) have drawn attention to the limited opportunities in otological surgery which the young surgeon gets nowadays from the small number of emergency mastoid operations. This alteration in the schooling of the apprentice—the cornerstone of training in a practical art—is particularly important in the surgery of the facial nerve. The actual technique of uncovering the nerve can be acquired by practice on the dry temporal bone but without intimate knowledge of the changed appearance brought about by pathological processes operations on the nerve can be hazardous. In trauma from mastoid surgery, gunshot wounds or fracture, as also in operations for chronic otitis media complicated by facial paralysis, the normal landmarks may have disappeared. Magnification is, of course, a powerful assistant in all these operations. When operating in acellular bones the proximity of the facial nerve can often be judged by troublesome pulsating bleeding from the stylomastoid artery.

This artery has recently acquired a new importance from suggestions that Bell's palsy may have its cause in primary ischæmia from vasospasm. It has even been said that the lower part of the nerve has a poorer blood supply than the horizontal part and that ischæmia in the region near the stylomastoid foramen has a poor chance of collateral relief. Michael Blunt (1954) of the Anatomy Department of the Royal Free Hospital has recently investigated the blood supply of the facial nerve—both the gross vascular pattern and the interfascicular plexus.

It appears that the characteristic feature of the blood supply of the facial nerve is the free connexion of vascular channels, both by direct arterial and venous anastomosis through the petrosal and stylomastoid vessels and by the intrinsic longitudinal plexuses of the nerve trunk.

This information that the blood supply of the facial nerve is not precarious has been given to us as a result of an exact scientific investigation. How that information is to be used in solving the problem of Bell's palsy remains in the province of our practical art.

REFERENCES

BLUNT, M. J. (1954) *J. Anat., Lond.*, **88**, 520.
College of General Practitioners, First Annual Report (1953) *Practitioner*, **171**, suppl.
DAHLBERG, G., and DIAMANT, M. (1945) *Acta otolaryng., Stockh.*, **33**, 378.
FORMBY, M. L. (1945) Medical Research Council, Report No. M.S.D. 17.
FRIEDMANN, I. (1954) *Proc. R. Soc. Med.*, **45**, 942.
General Register Office (1954) Studies on Medical and Population Subjects, No. 8. Measurement of Morbidity. London.
JOHNSTON, C. M. (1948) *Brit. med. J.*, ii, 1049.
LEWIS, R. S., and GRAY, J. D. (1951) *Brit. med. J.*, ii, 939.
MCGUCKIN, F. (1953) *Proc. R. Soc. Med.*, **46**, 371.
OJALA, L. (1950) *Acta otolaryng., Stockh.*, Suppl. 86.
PATEY, D. H. (1952) *Proc. R. Soc. Med.*, **45**, 25.
RUTTER, P. E. H., and BALLANTYNE, J. C. (1952) *Lancet*, ii, 314.
SEED, G. S. (1950) *J. Laryng.*, **64**, 700.
SIMPSON, R. R. (1954) *Proc. R. Soc. Med.*, **47**, 205.
SPENCE, J. C., WALTON, W. S., MILLER, F. J. W., and COURT, S. D. M. (1954) A Thousand families in Newcastle upon Tyne. London: Nuffield Foundation and Nuffield Provincial Hospital Trust.
THORBURN, I. B. (1954) *J. Laryng.*, **68**, 739.
TÖRÖK, M. (1937) *Zbl. Hals-, Nas.- u. Ohrenheilk.*, **29**, 121.
TROTTER, W. (1941) Collected Papers. London.
TUMARKIN, I. A. (1953) *Proc. R. Soc. Med.*, **46**, 379.

Section of Psychiatry

President—W. MAYER-GROSS, M.D., F.R.C.P.

[*December* 14, 1954]

A Children's Unit in a Mental Hospital. Treatment and Research

By W. J. BLACHFORD ROGERS, M.A., M.B., M.R.C.P., D.P.M.

THE first Children's In-patient Psychiatric Unit was started by Bleuler in Zurich, in the grounds of a mental hospital. Later this Unit was removed from the hospital, and the children cared for by educationally trained workers under the direction of a psychiatrist. In England an In-patient Children's Unit was started at Mill Hill under Dr. W. H. Gillespie in 1944, the Unit later re-starting at the Maudsley Hospital. There are now similar Units at St. James' Hospital, Portsmouth, at Mapperley, and at Hill End.

The Children's Unit at Crichton Royal was started in 1951. It is contained in three separate houses close together and outside the grounds of the main hospital, each holding about 20 children. The original house, Ladyfield, is a moderate-sized country house standing in its own grounds.

Ladyfield houses 20 children, usually 12 boys and 8 girls, their ages ranging from 5 to 14, and their I.Qs. from 80 to 150 or over. (Children of below average intelligence are admitted to another part of the Unit.) The problems of the Ladyfield children range from those presenting as mainly educational difficulties to those whose disturbances are due in the first instance to organic damage to the central nervous system; in between, and forming the majority of the cases, is a group of maladjusted children, who may be constitutionally vulnerable, but in whom environmental stresses appear to play a large part in the causation of their disturbances.

The lives of the children in Ladyfield are based on the regime found in normal residential schools. For this group of 20 children, the Local Education Authority supplies one full-time and one part-time teacher. The children's day is based on an ordinary school day. They work in small groups, and a child is expected to be doing something during each period from 9 a.m. to 3.30 p.m. The particular activity may be a free play period, and there is great flexibility in the application of the school programme to a particular child's needs. In a disturbed phase a child may do as little as one hour's formal schooling a day, or, very occasionally, no school for a few days, but most children, including those with psychotic illnesses, do at least two hours' formal schooling from the time of their admission, and work up gradually to a full school day. The remainder of the school hours are spent in occupational therapy, woodwork or sewing, in small groups. For children too disturbed to be in school, or needing for a few days almost constant individual attention, we sometimes devise a special course, which may be called "domestic science" and which means, in fact, that the child has one nurse to himself for most of the forenoon.

After school hours there are various activities. On Mondays a bus takes the children to the sea-shore or into the country—a few quite genuine volunteers remaining behind in school. On Tuesdays and Fridays the children go swimming with various members of the staff. Here the children overcome an anxiety situation in close physical contact with those looking after them. These swimming days are the only occasions on which the children go inside the main hospital grounds. On Wednesdays the children go into the town in groups with members of the staff in mufti, to spend their pocket money, 1s. 6d. being the limit. On Thursday there is a percussion band run by one of the psychologists, and on Saturday forenoon there is a visit to the children's cinema in the town. On Sunday, as we live in Scotland, almost all children go to church, again to the town, in small groups to the particular church to which they belong.

All these activities are voluntary. This kind of life may appear too highly organized and disciplined for the treatment of disturbed children, and so it would be if the programme itself were not highly flexible. We have found that, in fact, children feel more secure with a regular routine, if only because they can rebel far more effectively if there is a framework against which they can revolt. To make such a framework sufficiently pliable, it is essential that all members of the nursing staff should know the stage of treatment of each child—to know from whom to accept a withdrawal from group activities, and whom to encourage to join in; which of the children need a very permissive atmosphere, and which are secure enough to respond to gentle social pressure. All true discipline is based on the implicit bargain the child makes with an adult—"I will give up this particular gratification in order

to retain your approval, which I value more". With most children, a period of full and unqualified approval is necessary before relationships with adults become sufficiently secure for this implicit bargain to have any meaning for the child.

When a child first comes to Ladyfield, he usually settles down very quickly. He finds security in the regular though not rigid routine, and in the tolerant, and, at first, very permissive attitude of the staff, and from the security of the staff themselves, gained from experience and real liking for children. Affection is demanded and given constantly by all and sundry. Individual therapy usually begins towards the end of their settling down period, which may take a month or more. Play is the normal medium of communication of younger children, but in all cases the therapist aims at reaching a stage when the child's problems can be discussed with him in terms of relationships and events in the immediate present. His reactions to the immediate situation can then be discussed in relation to the family situation.

In order to carry out this therapeutic plan effectively, it is necessary that all members of the nursing staff should know the family background of each child, the phase he is going through at that particular time (a completely permissive attitude to all children would lead to chaos and great insecurity among all the children), and the particular stage of the individual therapy. A very high standard of nursing is required. The necessary data are given to all the nurses at regular weekly discussions with the doctor. At these discussions also, the nurses, including the most junior members of the staff, are encouraged to talk freely about the children. The doctor obtains information in this way—little incidents, of great significance, which never get through to the regular daily reports. Particularly important is the information provided by the junior members of the staff, who spend most time with the children, and who see aspects of their behaviour hidden from the senior staff.

The same close liaison is maintained with all other workers who come in contact with children, occupational therapists, &c., who also have regular weekly discussions with the doctor.

The educational psychologist, a member of the hospital staff, is responsible for the psychometric testing of the children, projection and attainment tests. He works in the closest contact with the doctor and the teachers in integrating the school programme and arranging the groups of children for teaching and other activities. He advises the teachers on aspects of remedial teaching, and carries on a share of the individual psychotherapy. Research projects are planned with him.

The nursing staff for this part of the Unit consists of 3 senior staff, 3 assistant nurses, and 5 cadet nurses, girls of 15 to 17. The senior staff includes the assistant matron to the Unit, who also acts as Sister to Ladyfield; a male charge nurse; and a male deputy charge nurse. The assistant nurses are 2 women and 1 man. They work with the children and do a share of the domestic work, as also do the cadets. All the domestic work is done by the nursing staff. Ward-maids and other workers, if used in a Children's Unit, are often recipients of confidences, and form important relationships with children, while remaining outside the therapeutic situation. The cadet nurses, who work for one to two years in the Unit before starting their training in the main hospital, do a very important job. They play well with the children, and also act the roles of older siblings. Recently, one of them came running in, saying "We have had a lovely game of Indians"—and she quite obviously had. Their youth and energy are great assets, and their quickness of response and their own incomplete development bring out strong reactions in the children which are used therapeutically. Student nurses are only used in the Unit occasionally, as extra hands. The three months they usually spend in a ward is too short for work with children; important relationships are formed only to be broken.

At the end of each week there is a staff conference attended by the assistant matron, the charge nurse and deputies, the teachers, the educational psychologist, the P.S.W. and the doctor. Here information is pooled, and decisions taken as to methods of treatment, composition of the various groups, discharges and admissions.

An example of the organic kind of difficulty, together with emotional problems superimposed on it, is that of a boy, Lester, who developed normally until the age of 7, when he developed tuberculous meningitis. He was treated with streptomycin, which left him stone deaf, with major and minor fits, and very severe temper tantrums when faced with the least frustration. Performance tests indicated that his intellectual ability was unimpaired. He became impossible to nurse in the sanatorium, and also at home, and was admitted to Ladyfield. After a few months he settled down very well, took part in all the practical activities such as woodwork, and with all the social activities of the other children. His fits were controlled and he even learned to swim. He is now sufficiently well adjusted for his transfer to a school for deaf children to be considered.

The problem of the child whose disturbance appeared to be caused in the main by environmental stresses, is well illustrated by the case of Irene. She was 8 when she was admitted

to Ladyfield. She was the middle one of three daughters, and she had been born after the father of the other two had been serving in the Forces abroad for over a year. She had been completely rejected by both father and mother. Her symptoms included enuresis, encopresis, behaviour which was described as autistic in the referral letter, difficult behaviour and backwardness at school, and an almost complete withdrawal from ordinary personal relationships. She settled down fairly quickly on admission to Ladyfield, and most of the symptoms, such as encopresis and enuresis, soon disappeared. She then caused no trouble in the Unit, but wandered round alone, not mixing with the other children, and when in trouble, going off on her own to cry. Her individual therapy then started, and I saw her daily for about an hour.

I am going to give here some details of the individual treatment, and then describe how this was extended to the total situation.

At first she chattered rather inconsequently and played with the animals in the sand-tray, remarking at times "Fathers never have much to do with families, do they?" On one occasion she made a circus, with a fence round it. I put two plasticine figures, to represent her sisters, outside the fence to watch. She at once changed the play, made a coach, and put in it figures representing the Prince, Princess and Cinderella; I asked her if she would like to be Cinderella and she said she would. Later, she painted pictures of a castle with the good people shut up inside by the bad king and his people. In front of the castle was a maze, which was the way out. The only people who could show you the way out were the witches, and when they got you through the maze, they ate you.

At the end of about four weeks, I found her crying in bed one evening. Her crying was unlike that of most of the children in the Unit, who, after a short time, were sufficiently secure to express a good deal of aggression mixed with their grief. She came to my room and after a number of evasions she told me what she was crying about. She said "I am crying because I'm never going to have a happy life." I asked her why. She said "My family don't want me; if your family don't want you, nobody wants you, and if nobody wants you, you will not have a happy life." I agreed that the situation with regard to the family was bad, but said that I would not regard it as hopeless. I had seen children as unhappy as she was then accepted fully into the family again. I also said that we must face the fact that the family situation might not improve, but did that necessarily mean a life of unhappiness? I quoted her own choice of Cinderella to her, saying that Cinderella's happiness had come from outside the family. From this we talked about Irene herself—was there any chance of people liking her. She said no she was ugly. She had some time previously said that ugly children always grew up to be pretty, so that was discovered to be an asset. We talked about her other assets, and then got down to her relations with people in her immediate environment. Who liked her? She thought I liked her a little, but no one else really liked her.

At this point I suggested to Sister that she came more into the picture. Sister, the most important mother figure in the Unit, has a gift for making a child feel she is the only one in Sister's life, without the other children noticing or feeling jealous. When Sister began to make a special fuss of Irene, Irene found that one of the best ways of getting Sister on her own for three-quarters of an hour was to ask to go out of school and not come back. The Schoolmaster, through the regular staff conferences, knew what was happening, and made no comment when eventually Irene returned. Irene's behaviour on parting from Sister at this time illustrates her strong attachment and her remaining uncertainty. She would go out of the room, immediately return and run to Sister, saying "I have forgotten something". She would then hug and kiss her and run out. Irene now had a very good relationship with Sister and with me. Then came a report of trouble in the girls' dormitory, where Irene slept, with three other girls—one older, two younger. Irene had got the two younger children on her side, and was making life very miserable for the older girl. This situation was allowed to develop, but another member of the staff, not Sister, was detailed to pay special attention to the older girl, who was the outcast of the group. After a short time, Irene had made it up with the older girl, and had got the others up against one of the younger ones. The younger one's extra needs were met by yet a third member of the nursing staff. At this point I asked Irene at one of my interviews with her what it felt like to have Pat (that was her younger sister) under her thumb. Irene saw the point at once, and said it felt very good. Soon she was on very much better terms with the other children and was playing freely with them. She was much brighter all round. In the early stages of her treatment she was very nervous of swimming and often asked if she could have her interview with me during the swimming time. This I always agreed to. As she gained confidence, she started to go swimming again, asking if she could see me afterwards. She soon learned to swim and enjoyed this as much as the other children. Her school work improved and then after a few weeks, the Schoolmaster reported that Irene was becoming very difficult. She caused disturbance in school and often refused to do any work. After a comparatively short negativistic phase with him, she settled down again and began to work better than

ever. The same thing happened with the Occupational Therapist even later than the Schoolmaster problems. The Occupational Therapist reported one week that Irene, who had always been one of the best workers, seeking approval in a not very animated way, had become very difficult, saying that everything the Occupational Therapist suggested for her to do was stupid and that the Therapist should have seen that this was not the kind of work a left-handed person could do. This testing-out behaviour is, of course, very common with children, and if rejection is to be avoided, with risk of a setback, all the staff must know what is happening to the child. With Irene, the home situation remained bad, but in spite of this, she continued to improve in all fields of activity. She no longer wanted daily interviews with me, but would say "I will come and see you again on Tuesday" (perhaps three days' time). If in the meantime she was in any kind of trouble, she at once demanded to see me. She would then come straight out with her difficulty, and we would discuss it.

In such a closely integrated Unit a great deal of information about the child's behaviour is available, and in particular his relationships to adults and to children. All the evidence suggests that it is very difficult, if not impossible, for the individual therapist to assume the roles of all the people who affect a child's emotional development. Children, even though they are severely disturbed, have a much greater capacity for immediate and varied response to particular situations than adults, and show a much greater capacity for adaptation, and for developing new patterns of behaviour. They respond quite differently to men, to women, and to other children, and seem to need a real individual of approximately the correct age and sex, with whom to work out their own particular problems. The therapeutic approach to the child is oriented round, and determined by the individual therapy, but however intense the relationship of the child is to the therapist, we are continually reminded that it is *not all-sufficient*, the child still reacts violently and specifically to other individuals. This experience is contrary to the all-embracing concept of transference relationships in children.

The same methods of treatment, based on intensive individual treatment, but attempting to bring all members of the staff into the active therapy, and to use each situation as it arises to further the general plan, have been used *with psychotic children*. The results are, so far, very encouraging—though it is much too early to see the end-results. The prognosis in these cases is notoriously poor, and we may so far have achieved no more than a fair remission. What we *have* done is to advance well beyond the stage of a better adjustment in a more protected environment—almost always possible with psychotic patients—to a markedly better adjustment outside hospital, with much warmer relationships with people.

When speaking of active treatment involving the whole staff, it must be made clear that the nurses do not take over or encroach on the role of the psychotherapist; this is ensured by the close link they have with the doctor. It is interesting to note that as the understanding by the nurses of the children's problems has grown, punishments have become less and less, each upset being dealt with by a nurse individually in terms of the child's own difficulty. The only punishments now in use are mild deprivations, such as the privilege of going to town with pocket money for one week, and even this is only used during the later stages of a child's treatment, as a mild form of social pressure, when he is secure enough in his relationships with people to accept it. The very occasional protests of other children at apparent discrimination are readily understood by them in terms of "You have been here longer" or "You are getting on so well, I think you could have coped with that situation better". So skilful are the members of the nursing staff at handling these problems that I am hardly ever myself faced with a disciplinary problem, a great asset from the point of view of individual therapy.

The case of a psychotic boy called John shows these methods applied to this type of case. John was 7 on admission. His development and his state on admission fitted very well with the group of children described by Kanner as "infantile autism"—a condition now regarded by him as schizophrenic.

This boy's behaviour was so odd that he stood out from the other children. He spent most of his time wandering round, sometimes laughing in a detached, inappropriate way, and holding up two sticks to represent the hands of a clock. He did not play at all with the other children, and made no spontaneous approach to adults. He quickly adapted himself to the routine, in fact he became very upset by the slightest deviation from it. His speech was infantile, and he always referred to himself by name—"John wants"—"John not do so-and-so". He was untestable by any full-scale psychometric tests, but some performance tests in which his interest could be aroused hinted that his I.Q. was probably somewhere between 130 and 140. He knew his multiplication tables up to 24 times and could tell the time instantly from a glance at a wrist watch.

For the first three months he remained a very odd, withdrawn child, and showed no inclination to make any normal contact with other children. He did show signs of developing a superficial relationship with members of the nursing staff at about a 2-year-old level. He learned the names of the nurses, and would try to tease them into chasing him by calling

them by the wrong name. In school he worked fairly well in a stereotyped way, and began to demand individual attention from the teacher.

At this stage intensive individual therapy was started with a woman doctor. With her, he hardly ever played with toys. He wandered round the room, repeated what she said to him in a manner suggestive of echolalia, but occasionally responding appropriately. At first he would only stay with her for ten minutes at a time, asking to go to the toilet and not returning. After a few days of this behaviour he would ask to go out but would then return and stay with the doctor for a few minutes longer. Eventually he would stay with her up to three-quarters of an hour without asking to leave during the session. He began to sit on the edge of her chair, but if invited to sit on her knee said firmly "No". Then he began to climb on her knee, to show a great interest in underwear and in breasts. He became very much more friendly in his manner, and would carry on little disjointed conversations. At this time, after about two months of therapy, his parents paid one of their monthly visits—they lived 200 miles away. For a few days before their visit John became more withdrawn. They noticed no change in him since admission. During the week following their visit John recapitulated with the doctor the stages he had gone through during the previous two months, starting with a ten-minute session, and ending up sitting on her knee, demanding affection. The parents were advised not to visit for three months—the only time this course has ever been adopted in the Unit, which has no set visiting hours—parents are encouraged to visit as often as possible. During this three months John's progress with the doctor continued, and he gradually developed superficial relationships with other members of the staff, with whom he would play if they made the advances. Left to himself, he relapsed into his fantasy world and wandered round with his two sticks. Towards the end of the three months he would sometimes play with another child.

At the end of three months without visiting, the parents came again. John made his first positive approach to them, and his progress with the doctor was described to the mother. She had previously rejected him, and had always shown evidence of much guilt in her feelings about him. This time she took him off on her own and cuddled him, returning next day to say that she wanted to take him home and cuddle him some more. She was surprised and delighted when she was told she could take him home for as long as she liked, and he went off for a month's holiday—extended later to six weeks. During this time she coped very well with his infantile sexual curiosity until it reached an aggressive phase, and then began to withdraw from him. Towards the end of the holiday he wanted to return to Ladyfield, and began counting the days. On his return, John's problems were further explained to her and it was decided to give him another three weeks' holiday at home in six weeks' time. His therapy at Ladyfield continued, the relationship with his doctor progressed, and he began to play better with other children. His school work was now more productive, and less stereotyped. The second holiday was an even greater success, but his mother was rather perturbed by a hint of a shift of the expression of his curiosity towards genitalia. John now almost passes for a normal boy, is much more lively, and plays quite well with other children. He still occasionally repeats things said to him in echolalia fashion, and at times appears withdrawn, but most of the time has fair contact with his surroundings. His individual treatment by the same woman doctor continues, and he is now working out with her the problem of his infantile psycho-sexual development, still at a very early stage.

In this case the progress of the individual therapy has been stressed, and certainly John's relationship with the doctor was far more intense and personal than his relationship with anyone else; and it was the demonstration to the mother of the child's capacity for giving and accepting affection which caused the release of her own maternal feelings and enabled her to give them expression. Nevertheless a very great and constant effort was necessary by all members of the staff to keep John in contact with reality; and it is very doubtful if without this all-out effort by the whole staff the individual therapy could have succeeded. The nurses had to be reminded constantly that John must never be left for long on his own. It was very easy to forget about him, as he caused no trouble, while dealing with more boisterous and demanding deprived children, but only people paying individual attention to him kept him in touch with his surroundings. This task is now becoming progressively easier. He has begun to talk about home, and for the first time wants to stay at home; previously he had always expressed a strong desire to return to Ladyfield whenever he was away.

This case also illustrates another very important aspect of the work of the Unit, the attempt to modify the child's environment; in most cases, the family. In this particular case the parents were seen by me, but in the great majority of cases this work is done by the P.S.W. As has been stated, there are no visiting hours in Ladyfield, but most parents find it more convenient to visit at week-ends. For this reason the P.S.W. takes his time off in the middle of the week, and is there to see parents on Saturdays and Sundays. He keeps

in close touch with the progress of the child in the Unit. The parents are brought into the picture from the beginning, the attitude being not that admission to hospital means taking your child away and curing him and then handing him back, but, "You have a problem, we are prepared to share that problem with you, and to try to work it out with you". The importance of this aspect of the work cannot be over-emphasized. Our experience—and of course that of many others working in this field, shows that however successfully a child may work through his problems in the Unit, unless these problems are worked out successfully in the home as well, the results of treatment are disappointing. At the same time there is abundant evidence that mere separation of the child from his home, and placing him in a more favourable environment without active treatment is unsuccessful in the majority of cases severe enough to warrant admission to Ladyfield.

Most children come from families still functioning as families, and go back to their families. Some come from institutions, and in these cases attempts are made to work with those responsible for the child in the same way as the work is done with the parents. The children go for their holidays to the institution, which is, after all, their home.

The work of the original part of the Unit, Ladyfield, has been outlined. A very similar house, now called Ladyfield West, has space for a further 15 children. These children are very similar to the original Ladyfield group in their intelligence and the nature of their disturbances, except that hyperactive or very destructive children are not treated here. The atmosphere is quieter, and the children are given more responsibility for their affairs. They have their own teacher, and form a more stable group with which class work is possible.

The third part of the Unit, Hannahfield Hall, has 23 children aged 3 to 16, together with a few older handicapped patients. These children suffer from all degrees of mental and physical handicap; from children of idiot level, with or without physical handicap, to disturbed children of normal intelligence with physical or psychiatric disorders of such severity that they are unable to fit in with the very active life of the children in the other two houses. Examples are, a girl who is mentally defective, blind and spastic, and a boy of 11 of normal intelligence who became completely withdrawn in a catatonic state. Here less is expected of the children, but there are facilities for developing their capacities, and for treating their psychological problems along the same lines as in the rest of the Unit. Some children from Hannahfield attend school and various other activities, with the Ladyfield children. For example the psychotic boy just mentioned improved under this regime until now he spends all his days at Ladyfield, attending school, &c., and only sleeps at Hannahfield. This is a recent development, but the results are so far very encouraging, and it enables treatment to be offered to any disturbed child, irrespective of his basic mental or physical equipment. In our view mental deficiency is part of, and closely connected with, child psychiatry.

Conclusion

The objects of the Children's Unit are—to provide an environment which combines as much as possible of the family influences and the school with hospital facilities, so that observation and treatment can be carried out under conditions where as many normal activities and influences as possible are available. The family setting can only be partly reproduced, but the limitation of the separate houses to 20 children, the very individual approach of the nursing staff, and the presence of Sister as a mother figure, as already indicated, together with the male charge nurse, who fulfils admirably the role of father, all combine to provide many of the essential family influences on the child. The school side is well catered for, all facilities of a good residential school being available. The hospital supplies all the facilities for investigation, EEG laboratory facilities, &c., together with a regular staff with psychiatric training. If these objects are fulfilled, this setting offers very good opportunities for research into children's psychiatric disorders.

From the point of view of research, one of the problems in such a closely integrated Unit is that the mass of detailed information available about children, valuable as it is, is extremely difficult to handle for purposes of comparative, or even of individual studies. An attempt to solve this problem has been to arrange a special research folder in addition to the ordinary case notes. The ordinary case folder will contain the whole mass of information about the case, individual interviews, P.S.W. reports, correspondence, &c. The research folder is to contain a definitive summary of all that is known about the case, together with summarized data concerning all aspects of a child's behaviour, including relationships with adults, with other children, performance in school, &c., recorded weekly. This summary of the detailed observations of behaviour gives an idea of the manifest picture of the disturbance; its links, if any, with particular environmental stresses, and with treatment—drugs, psychotherapy, &c.—can be determined.

Another serious problem, common to all psychiatrists, is that of semantics. After two years the staff has acquired a common body of experience, and a mutual understanding

We have tried to record accurately and simply the children's behaviour, including their reactions to various members of the Staff and to other children; and to keep in mind the distinction between observed behaviour and its interpretation. Cases like that of Irene have encouraged us to use this method of tabulating data in the form of a behaviour chart. Many other children show similar patterns of behaviour, forming relationships first with senior members of the staff, male or female, then junior staff, and finally other children. We have been struck by the way the children pick out particular members of the staff in accordance with their current needs, and work out their problems with them. The more intensive the individual therapy, the more varied and intense their response to other people becomes. It was the realization of this which forced us to bring all members of the staff into the therapeutic situation, and to be prepared to work out a particular problem with a child individually as it occurred, in the heat of an emotional upset.

In addition to the study of personal relationships, there is need for further study of the natural history of childhood disorders. Some progressions are well recognized, as the case of the child short of affection and security who starts by clinging and when repulsed shows destructive or other disapproved attention-getting mechanisms; more severe punitive measures with continued shortage of affection may result in the appearance of underhand manifestations of disturbance, lying and stealing, possibly encopresis; further punishment may produce either a withdrawn rather hopeless child, or a rebel delinquent. There are, of course, countless variations on this over-simplified theme, but it is possible to recognize some of these patterns, and in this partly controlled environment to predict with fair accuracy the next phase in a child's behaviour when, as a result of treatment, the train of events is reversed. This is very helpful, since, as is well known, the beginning of psychiatric improvement in a disturbed child does not always mean better behaviour in a social sense, the opposite often being the case. A good example of the process just described is the case of Bruce, who had been encopretic for five years, when he was admitted at the age of 11. Within three weeks of admission to the Unit his encopresis was replaced dramatically by violent aggressive behaviour. When he went home for a week-end his mother was horrified, in spite of our explanations; she said "It was wonderful to cure his soiling so quickly, but I would much rather have had him as he was." We did not discover why the aggression meant so much to her until some time later, when we found out that her husband, whom she had always described as a rather ineffectual man, had served prison sentences for violent assaults on her. Bruce took some time to work out his anxiety and aggression in the Unit, and even longer to work them out at home.

If we succeed in obtaining good information about the child's reactions in this environment, the next problem is to see how the child deals with stresses in his home environment when he returns to it. It has already been shown, in the case of John, that we attempt to bring the family into an active part in the child's treatment from the time of admission. Several of our recent cases have shown the great need for after-care. On the basis of the close link with the family established during the child's stay in the unit we hope to carry out long-term personal follow-up, extending, if possible, for about twenty years. The importance of such a follow-up, if in any way practicable, is obvious. Firstly it gives us an idea of the effect of treatment in the Unit, whether we have merely achieved a temporary good adjustment in a protected environment, or whether we have achieved a real, if slight, change of direction which will enable the child to use his experience in the Unit to deal more successfully with the stresses of life outside. Secondly, it may well throw a little light on the origins of adult and adolescent neuroses. Much is talked in psychiatry of the effect of broken homes and unsatisfactory backgrounds. Here we have an opportunity of observing family stresses when they are actually operating, and their effect on the child.

A further extension of the sociological aspects of the work is an attempt we are making to study the problem of all children who experience a degree of maladjustment in a rural area. This involves very close co-operation of all the local authorities, and in particular the Education Authority. Through the Educational Psychologist employed by the Education Authority, it is possible to obtain information about all children who are maladjusted in school. We also wish to see the children dealt with by the Children's Officer, and all children who are brought before the courts. This again sounds an ambitious project, but the numbers in some of the neighbouring administrative areas are sufficiently small for us to deal with them. The next step will be to attempt to compare the development and environmental conditions of the maladjusted children, with a representative sample of the school population. This work can well be based on a large hospital in a rural area. Many of the necessary links with the local authorities are already there, including out-patient clinics run in co-operation with the local authorities. The in-patient unit is a valuable asset in this project for investigation and more detailed observation of specially difficult problems.

If it is agreed that psychiatric care is needed for the children admitted to Ladyfield, do the advantages of forming part of a mental hospital outweigh its disadvantages?

Here the question of who is to look after the children must be considered. In the Unit, teachers, occupational therapists and nurses all work together, playing different roles in relation to children. Teachers, by the very nature of their work and training, have to try to get a child to attain certain standards, in which attainment tests show clearly the child's performance in comparison with other children. However tolerant and understanding the teacher is, full approval can never be given to a child who is working below his capacity. The teachers in the Unit are, as we have seen, in close touch with the therapeutic plan for the children and are quite capable of working through a negativistic phase with a particular child in a therapeutic sense, but they do not lose sight of the basic fact that they are there to teach the children. This orientation, inherent in their profession, makes them less suitable than nurses for ministering to the basic needs of children—providing a great deal of affection, often in the form of close physical contact, feeding them, clothing them, putting them to bed, and joining in their play. A nurse's orientation is towards caring for people who, because of infirmity, need help with these basic functions—much closer to a maternal attitude than that of a teacher.

This difference between the didactic approach of the teacher and the individual and more maternal attitude of the nurse, is not readily appreciated unless one has the opportunity of observing these different people working with the same group of children, and the reactions of the children to them. Occupational Therapists sometimes find it difficult to steer the middle course which the nature of their work demands. They learn certain skills, which they teach patients, and in teaching these skills adopt a certain therapeutic attitude. They are not bound down by the curriculum and attainment levels of teachers, can give patients a wide choice, and can give much treater approval to indifferent work. In the Unit the children's O.T. varies from messing about with clay, or whitewashing the walls, to more orthodox activities such as basket-work or weaving.

The early emergence of aggressive phases of behaviour is sometimes seen with the Occupational Therapist, who because of her training to work mostly with groups, has a certain detachment. One boy made a puppet of his father and cast him violently into the dustbin some time before he got to the stage of having it out with his doctor. Some Occupational Therapists, however, concern themselves with such basic functions as feeding and elimination, which I can't help thinking are better dealt with either by the nursing staff in the ordinary course of events, or, if occasion demands it, by the doctor in the course of individual therapy.

If the case I have made out for the employment of nurses to look after seriously disturbed children is considered reasonable, the attachment of a Children's Psychiatric Unit to a mental hospital becomes almost a necessity. This is very exacting—though very rewarding—work, and by no means all men and women who make good mental nurses can cope with disturbed children. A large pool of first-class nursing staff is necessary, so that nurses can be given a trial period in the Unit, ostensibly as part of their experience. If they are not settled there, they can readily be moved to another ward without distress to themselves or to other members of the Unit.

From the point of view of having access to all the facilities and ancillary services, such as a large O.T. department, the link with a large hospital has very real advantages.

From the doctor's angle, the advantages are equally obvious. I find that discussions of my problem with other doctors working with adults is most valuable. I am helped by the healthy critical approach of experienced colleagues who are, quite rightly, intolerant of jargon, or loose concepts; and the danger, a real one, I think, of child psychiatry becoming a kind of esoteric cult is minimized. The other alternative for a hospital setting of a children's psychiatric unit, that of a link with a pædiatric hospital, would be highly desirable from many points of view, and there can be no question that child psychiatry must maintain the closest possible link with pædiatrics. For In-patient Units, however, there are grave objections to such a link. The needs of physically sick children and of disturbed but often hyperactive children are in almost all respects diametrically opposite, and cannot, I think, readily be reconciled. The need for a pool of nurses with psychiatric training has already been mentioned.

As regards research projects, while it is possible that the clinical research into the nature and origins of behaviour disorders already described might be carried out away from a hospital setting, research into the relationship of EEG to the observed disorders, and the changes in the EEG as a result of maturation or treatment can only be done in a properly equipped hospital. Similarly, research into the effect of drug treatment can only be attempted in a hospital setting with the aid of trained staff. The same considerations apply to the investigation of suspected organic cases, such as head injuries.

Finally, I think that to divorce child psychiatry from adult psychiatry would be illogical, and if it should occur, would be to the lasting harm of both disciplines.

Section of Experimental Medicine and Therapeutics

President—Professor CLIFFORD WILSON, D.M., F.R.C.P.

[*October* 12, 1954]

DISCUSSION: BILIRUBIN HÆMOGLOBIN AND CONGENITAL HÆMOLYTIC ANÆMIA

Dr. G. H. Lathe (The Bernhard Baron Memorial Research Laboratories, Queen Charlotte's Maternity Hospital, London, and The Institute of Obstetrics and Gynæcology, University of London):

Bilirubin Metabolism in Hæmolytic Disease

Under normal conditions hæmoglobin is released by the daily breakdown of about 1% of the body's red blood cells. The disintegration of this material involves separation of the protein, globin, from the four oxygen receptors. Each of these consists of a ring of four pyrrole groups and at some stage in the breakdown there occurs reduction and opening of the ring—yielding a fat-soluble yellow pigment, bilirubin. It appears that the body lacks the biochemical equipment necessary further to disintegrate, or re-utilize this material. It is disposed of by transformation to water-soluble pigments which are found in the hepatic secretion.

Although the precise change involved in the transformation of bilirubin to the pigment of hepatic bile is not yet understood, a distinction between two classes of pigment has been made, since the turn of the century, by means of the van den Bergh reaction. Bilirubin, the pigment formed in the reticulo-endothelial system and found normally in small amounts in human plasma, gives an "indirect" van den Bergh reaction, i.e. colour development takes place only in the presence of alcohol, or some other substance. In contrast, bile gives a "direct" reaction without alcohol. Although the difference in the type of reaction has frequently been attributed to a conjugation of pigment with protein, this possibility has now been excluded by the separation of these two types of pigment in protein-free form (Cole and Lathe, 1953).

Cole, Lathe and Billing (1954) have further shown that the direct-reacting material, found in the plasma of patients with obstructive jaundice, consists of two water-soluble pigments which they have called (direct-reacting) pigments I and II. It seems possible that pigment I is an intermediate in the transformation of bilirubin to pigment II, which is the most polar (water-soluble) of the three. Our present information regarding the relative amounts of bilirubin, pigment I and pigment II occurring in different conditions is summarized in Fig. 1.

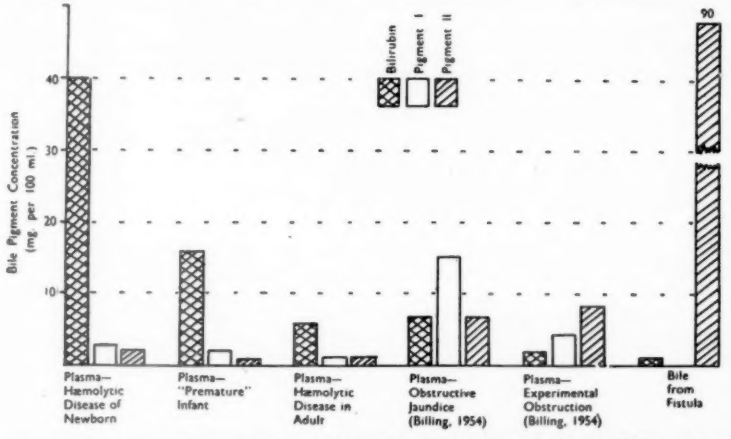


FIG. 1.—Examples of the relative amounts of bilirubin, pigment I and pigment II found in plasma in various conditions, and in fistula bile.

[The relative proportions of the two direct-reacting pigments, when they are present in small amounts, can only be estimated approximately.]

Pigment II is present in large amounts in fistula bile, which is almost free of bilirubin and pigment I. Pigment I is found in larger amounts than pigment II in the plasma of patients with biliary obstruction. Bilirubin is a minor component. Billing (1954), in noting that there was more of pigment II than pigment I in experimental obstructive jaundice in animals, has suggested that the predominance of pigment I in the serum of patients with obstruction is due to a secondary metabolic derangement.

Hæmolytic jaundice in the adult patient is characterized by a predominance of bilirubin over pigments I and II, but only exceptionally does the amount of bilirubin rise above 8 or 10 mg. per 100 ml. Thus bilirubin occurs in minor concentrations in adult hæmolytic disease, as well as in obstructive conditions.

In contrast, the plasma of infants with hæmolytic disease of the newborn, and of premature infants, frequently contains quantities of bilirubin of a much higher order. In hæmolytic disease it often rises to 30 mg., and occasionally reaches 50 or 60 mg. Among newborn infants the height to which plasma bilirubin rises in the neonatal period is determined in a large measure by the birth weight of the infant, as well as the length of gestation (Billing, Cole and Lathe, 1954). This influence of weight has been demonstrated throughout the range of birth weights of 2·5 to 9·5 lb. and is not confined to "premature" infants. In the latter a rise consistently occurs and levels of 10 to 15 mg. are very frequent. Concentrations of 20–30 mg. appear occasionally. Thus the small newborn infant and those with hæmolytic disease are in a different class from adult cases of hæmolytic jaundice, as well as obstructive jaundice, in respect of the amounts of plasma bilirubin which are found. This requires an explanation since the rate of hæmoglobin breakdown is no greater in hæmolytic disease of the newborn than that of the adult, and Mollison (1948) has shown that the hæmoglobin destroyed by the normal newborn infant is of a minor order.

It is possible to compare the liver of the newborn infant and that of the adult, with respect to their capacity to excrete bilirubin. From the studies of Weech, Vann and Grillo (1941) it is clear that with a plasma bilirubin concentration of 10 mg. per 100 ml. the normal liver could excrete the bilirubin equivalent to all the hæmoglobin in the body in a period of ten hours. (A pigment excretory capacity of the same order is indicated by the more direct measurement on rats (Weinbren and Billing, 1954).) Fifteen minutes would suffice for the excretion of the bilirubin produced daily by a newborn infant. Thus a newborn infant (without hæmolytic disease) in which there is a plasma pigment concentration of 10 mg. per 100 ml. must be able to excrete bilirubin at only 1 or 2% of the normal adult capacity. With this reduced capacity to excrete bilirubin is a limited ability to transform bilirubin to pigment I and pigment II since the plasma of most newborn babies is almost free of these pigments even when substantial amounts of bilirubin are present. This contrasts with the experimental animal in which the intravenous administration of large amounts of bilirubin is followed by the appearance of some pigment I (Billing, 1954). Lathe (1954) has suggested that this limited ability to transform bilirubin is the fundamental defect in the pigment metabolism of the newborn infant.

This extraordinarily reduced capacity to excrete bilirubin explains (1) the unusual amounts of bile pigment present in the plasma of newborn infants, (2) the enormous accumulation of bilirubin that may occur in the presence of a relatively mild hæmolytic process in the newborn infant, and (3) the great difference in this respect between the adult and the newborn baby.

REFERENCES

BILLING, B. H. (1954) *J. clin. Path.* In press.
——, COLE, P. G., and LATHE, G. H. (1954) *Brit. med. J.*, ii, 1263.
COLE, P. G., and LATHE, G. H. (1953) *J. clin. Path.*, **6**, 99.
——, ——, and BILLING, B. H. (1954) *Biochem. J.*, **57**, 514.
LATHE, G. H. (1954) *Symp. biochem. Soc.*, **12**, 34.
MOLLISON, P. L. (1948) *Lancet*, i, 513.
WEECH, A. A., VANN, B., and GRILLO, R. A. (1941) *J. clin. Invest.*, **20**, 323.
WEINBREN, K., and BILLING, B. H. (1954) Personal communication.

Dr. J. G. Selwyn (Department of Pathology, Postgraduate Medical School, Ducane Road, London):

Red-cell Defects in Congenital Hæmolytic Anæmias

Nowadays the vast majority of cases of hæmolytic anæmia can be readily differentiated into those of a congenital type and those of an acquired type. This differentiation has become possible mainly through the development of two methods of investigation. Firstly, a patient's blood can be examined by the Coombs antiglobulin technique for the presence of auto-antibodies which can cause the rapid destruction of the patient's red cells; and secondly, by using the differential agglutination technique of Ashby or by labelling red cells with radioactive chromium, the period of time can be determined for which any particular sample of red cells survives in the circulation of any particular person.

Most cases of acquired hæmolytic anæmia are characterized by the presence of auto-antibodies in the blood and normal red cells transfused to the patients are destroyed very rapidly. In contrast, patients with congenital hæmolytic anæmia have no auto-antibodies in the blood and normal red cells transfused to these patients survive normally with a mean cell life of 100 to 120 days. But if red cells are taken from such a patient and transfused to a normal person, the length of time for which they survive is shortened and the mean cell life may be as short as ten or even five days.

The failure of red cells to survive normally in a normal circulation is an indication that the cells are defective in some way. And so by these methods of investigation it has been established that the red cells of patients with congenital hæmolytic anæmia possess some inborn defect.

The defect, as well as being congenital, may be hereditary and manifest in several generations of a family.

A Classification of Congenital Hæmolytic Anæmias

(1) Hereditary Spherocytosis.
(2) Congenital Non-spherocytic Hæmolytic Anæmia, Types I and II.
(3) Hereditary Elliptocytic Hæmolytic Anæmia.
(4) Other "Atypical" Congenital Hæmolytic Anæmias.
(5) Mediterranean Anæmia.
(6) Sickle-cell Anæmia Group.

Hereditary spherocytosis is the commonest type in this country and the causal gene is inherited as a Mendelian dominant. The red cells are morphologically abnormal in that they are thicker and so more spheroidal than normal—the so-called spherocytes.

In congenital non-spherocytic hæmolytic anæmia—as the name implies—spherocytes are not found in the blood, although there are other morphological abnormalities of the red cells. This condition is less common than hereditary spherocytosis. Many cases have no family history, although some have an affected parent or sibling. There are several different types of congenital non-spherocytic hæmolytic anæmia and of the patients that Dr. J. V. Dacie and I have studied, 4 were found to be examples of 2 types, each type being represented by 2 patients. These two types were quite distinct from the others and we have classified them as Congenital Non-spherocytic Hæmolytic Anæmia, Types I and II. The other patients have been grouped together as "Other Atypical Congenital Hæmolytic Anæmias". In these patients the red-cell picture presented a different abnormality in almost every case—for example in one patient there was moderate macrocytosis and anisocytosis, and in another there were some unusually large macrocytes together with some very small and distorted microcytes (Dacie *et al.*, 1953).

In hereditary elliptocytosis the red cells are elliptical in shape and the causal gene is inherited as a Mendelian dominant. In most cases the condition exists as a harmless trait, the cells surviving for the normal length of time, but in some cases, for an unknown reason, the cells have a shortened life-span and there is an associated hæmolytic anæmia.

In Mediterranean anæmia there is an inherited defect of red-cell formation, the red cells are abnormally thin and have a low hæmoglobin content. If the condition is severe, the cells have a shortened life-span.

In sickle-cell anæmia there is an inherited defect in hæmoglobin synthesis, an abnormal hæmoglobin—sickle hæmoglobin—is present in the red cells.

I would like now to describe in more detail the defects present in the red cells in Hereditary Spherocytosis and in Types I and II of Congenital Non-spherocytic Hæmolytic Anæmia.

Hereditary Spherocytosis

Vanlair and Masius (1871) were the first to describe accurately the features of congenital spherocytes. These cells are smaller in diameter than normal and are thickened, having lost to varying degrees the biconcavities of normal red cells, and some having biconvex surfaces approaching the shape of a true sphere. The increased thickness is revealed in fixed and stained blood films by the cells appearing more deeply stained than normal.

Congenital spherocytes have certain abnormalities in composition—e.g. they have a higher hæmoglobin concentration and a lower potassium content than normal (Maizels, 1936; Selwyn and Dacie, 1954). They also have, because of their increased thickness, an increased osmotic fragility, and if sterile whole blood from a patient with Hereditary Spherocytosis is incubated *in vitro* at 37° C., the osmotic fragility rapidly increases even more. In addition the cells undergo spontaneous lysis or autohæmolysis much more rapidly than normal (Ham and Castle, 1940). This rapid autohæmolysis *in vitro* is of great importance because it probably occurs *in vivo* as well and accounts for the shortened life-span of the cells. The spleen is known to be able to filter off spherocytes from the blood

circulating through it and to retain them for varying periods of time (Emerson *et al.*, 1947; Young *et al.*, 1951). In other words the spherocytes tend to stagnate in the spleen and incubation *in vitro* probably imitates this stagnation fairly well.

To explain autohæmolysis, Ham and Castle suggested in 1940 that when blood was incubated *in vitro*, metabolites accumulated in the red cells and tended to increase the osmotic pressure inside the cells. As a result water would diffuse into the cells to keep the osmotic pressure normal and cause the cells to increase in volume. Gradually the cells would swell up into true spheres and finally burst. Spherocytes, being more spheroidal than normal cells at the beginning of incubation, would take less time than normal cells to attain the shape of true spheres and to burst, and consequently they would undergo more rapid autohæmolysis.

Recently Dr. Dacie and I carried out some work to test this hypothesis (Selwyn and Dacie, 1954). Sterile defibrinated whole blood was incubated at 37° C. for forty-eight hours, and in Fig. 1 are shown the mean results of testing the blood of 12 normal persons. The line marked "Osmotic Fragility" represents the osmotic fragility of the most fragile red cells and this fragility underwent a steady increase during the forty-eight hours. At the end of that time 1·5% of the red cells had undergone autohæmolysis. The mean cell volume (the initial volume being taken as 100%), instead of showing a continuous increase during the forty-eight hours, showed at first an increase and then a decrease to near the initial volume.

Also in Fig. 1 are shown the mean results of tests on the blood of 10 cases of Hereditary

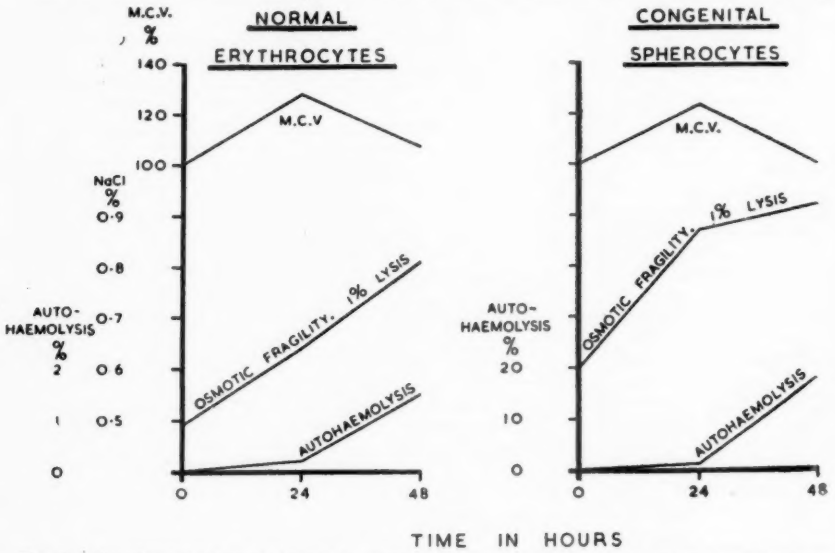


FIG. 1.—Autohæmolysis, and changes in osmotic fragility and in mean cell volume resulting from the incubation *in vitro* of normal red cells and of red cells from patients with hereditary spherocytosis. (Note the different scales for autohæmolysis.)

Spherocytosis. The initially raised osmotic fragility increased more rapidly than normal so that after incubation the most fragile cells were lysed by solutions of saline stronger than 0·85%. There was increased autohæmolysis (note × 10 scale)—17% of the cells had lysed at 48 hours. The mean cell volume again showed an increase at first and then a decrease to the initial value. Thus neither with normal cells nor with congenital spherocytes was there a continuous increase in cell volume, and moreover during the second twenty-four-hour period when autohæmolysis was more rapid than in the first twenty-four hours, the cells were actually shrinking. So the hypothesis of Ham and Castle did not appear to be true, and we were left with two problems to solve. Firstly, how did autohæmolysis take place, and secondly, what caused the cell volume to increase at first and then decrease again?

The cell-volume changes were found to be due to fluctuations in the cell sodium and potassium content. Maizels (1949, 1951)[1] has shown that energy derived from the metabolism of glucose normally keeps the cell sodium and potassium levels constant, but that *in vitro*, in the absence of glucose, sodium rapidly diffuses into the cells from the plasma and potassium diffuses out of the cells at a slower rate. This is what happened in our incubated samples

[1] *See also* FLYNN and MAIZELS (1949).

of normal blood because the normal amount of glucose initially present was quickly used up by the red cells. Sodium diffused into the cells more rapidly than the potassium diffused out, so that the total sodium and potassium content rose. Water also diffused into the cells to keep the osmotic pressure normal and so the cells increased in volume. But when we continued the incubation for a second twenty-four hours the potassium loss was greater than the sodium gain and so the total cation content fell, water diffused out of the cells and the cell volume decreased. If excess glucose was added to the blood samples before incubation, all these changes were retarded. Similar changes accounted for the volume increase and decrease with the hereditary spherocytes.

Now considering the autohæmolysis of the spherocytes again, I have pointed out that after incubation the osmotic fragility of the most fragile cells was such that they were lysed in solutions of saline stronger than 0·85%. This concentration of saline is within the normal range of isotonicity, which means that the spherocytes had almost, if not entirely, lost their ability to swell when placed in a hypotonic medium. Moreover, when the incubated spherocytes were examined under a microscope, they appeared as small spheres. As a result of these observations we believe that during incubation the cell membranes of spherocytes shrink irreversibly around the cell contents, thus turning the cells into small rigid spheres which cannot undergo any further change in shape or volume. Consequently, the cells cannot increase in volume when placed in hypotonic media and hence have a greatly increased osmotic fragility. Furthermore, because of these structural changes, the cells undergo rapid spontaneous lysis.

With normal cells we believe that similar processes occur but much more slowly.

Congenital Non-Spherocytic Hæmolytic Anæmia, Types I and II

The red cells of one of the two boys who were found to have Type I anæmia are shown in Fig. 2. The red cells of both boys were alike and they varied slightly in size with

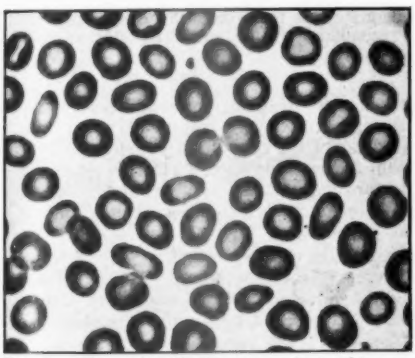


Fig. 2.—The red cells from a patient with congenital non-spherocytic hæmolytic anæmia, Type I. (×700.)

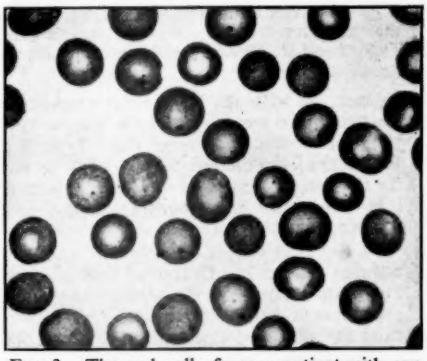


Fig. 3.—The red cells from a patient with congenital non-spherocytic hæmolytic anæmia, Type II. (×700.)

occasional macrocytes and oval cells. The Type II anæmia was found in a 30-year-old woman and a 13-year-old girl. Both patients had undergone splenectomy in early childhood with no effect upon the hæmolytic anæmia. The red cells are shown in Fig. 3—they were mainly rounded macrocytes with many Pappenheimer bodies. A very high reticulocytosis was also present, 50–80% of the red cells were reticulocytes.

The behaviour of both types of red cell during incubation *in vitro* is shown in Fig. 4. The mean results for the two boys with the Type I anæmia were all normal—the cell-volume changes, the increase in osmotic fragility and the autohæmolysis. However, we did detect an abnormality in behaviour which I will describe later.

In contrast, the results obtained with the blood of the Type II anæmia were markedly abnormal. The mean cell volume did not increase at all, it stayed constant and then decreased a little, while both the autohæmolysis and the increase in osmotic fragility were markedly increased. After twenty-four hours' incubation the most fragile cells were lysed in solutions of saline stronger than 0·85%.

These results show again the independence of autohæmolysis and cell-volume changes and that autohæmolysis is not due to swelling of the red cells. The absence of an initial increase in the cell volume was found to be due to a rapid potassium loss from the cells, which was probably a secondary manifestation of the markedly increased autohæmolysis.

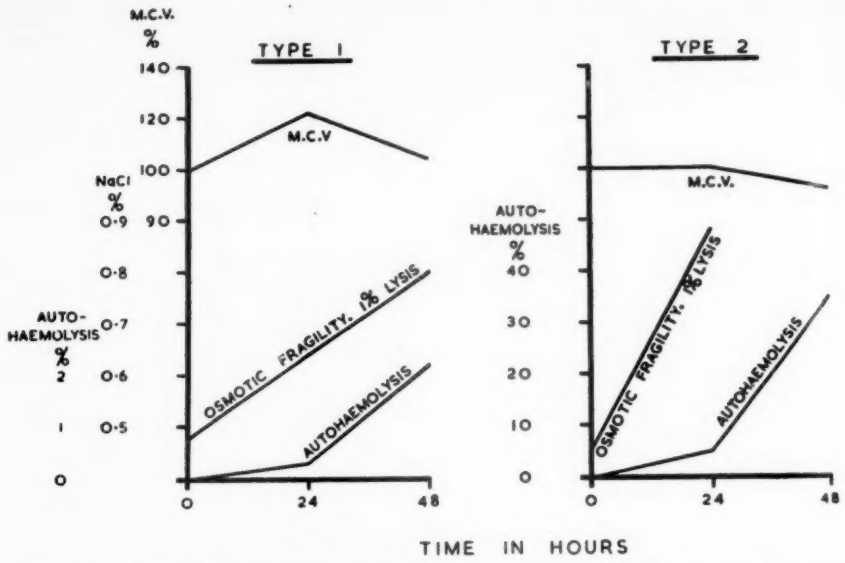


FIG. 4.—Autohæmolysis, and changes in osmotic fragility and in mean cell volume resulting from the incubation *in vitro* of red cells from patients with congenital non-spherocytic hæmolytic anæmia, Types I and II. (Note the different scales for autohæmolysis.)

In fact, as with the congenital spherocytes, the red cells of these patients were rapidly changing into small and fragile spheres through the shrinkage of the cell membranes. But the rapid autohæmolysis of these Type II cells and that of the congenital spherocytes were found to have different causes. Just as energy from the breakdown of glucose is necessary for the cation control of red cells, so is it necessary for the preservation of cell structure and it is well known that a constant supply of glucose to cells kept *in vitro* considerably reduces the autohæmolysis.

In Fig. 5 is shown the effect of adding an excess of glucose to a duplicate set of blood samples before incubation so that glucose was present throughout the forty-eight hours. Each point represents the autohæmolysis occurring in a blood sample without added glucose (abscissa) and in a duplicate sample to which excess glucose had been added (ordinate) to raise the glucose concentration to about 500 mg.%.

The open circles are the observations on normal cells. Without added glucose there was 0·5%–3·5% autohæmolysis and with added glucose there was no autohæmolysis or only minute traces. The solid circles are the observations on congenital spherocytes. The increased autohæmolysis is reduced by the added glucose but it is still very abnormal, and rapid autohæmolysis must play an important part in the destruction of spherocytes *in vivo*. To explore further the cause of the rapid autohæmolysis of spherocytes even in the presence of glucose, we tested the rate at which congenital spherocytes can utilize glucose and this was found to be normal (Selwyn and Dacie, 1954). Hence a defect presumably exists somewhere between the breakdown of glucose and the use of the resultant energy for the preservation of cell structure.

The hollow triangles are observations on the cells of the two boys with the Type I non-spherocytic anæmia. Glucose only slightly reduced the autohæmolysis. This was the only abnormality in behaviour that we detected in this type of cell, and what part this abnormality plays in the *in vivo* red-cell destruction is not certain.

In contrast, the results for the 2 cases of Type II congenital non-spherocytic hæmolytic anæmia, the solid triangles, were very striking. The addition of glucose did not reduce the autohæmolysis at all. This greatly increased autohæmolysis, even in the presence of glucose, is presumably taking place *in vivo* as well, and the very high reticulocyte counts in these patients indicate that there is, in fact, a very rapid rate of red-cell destruction *in vivo*. The failure of this last type of red cell to benefit from the presence of glucose was explained when it was found that these cells were only able to metabolize at about 25% of the normal rate.

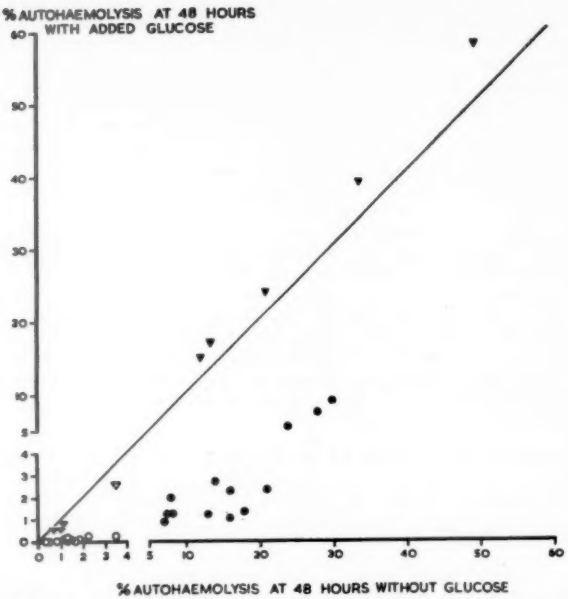


FIG. 5.—The effect of added glucose on the forty-eight hour autohæmolysis of different types of red cells. (For explanation *see* text. In the absence of any effect, points would fall on the diagonal line. Note trebled scale for normal range of autohæmolysis.)

Consequently in this type of red cell, the supply of energy from the breakdown of glucose is deficient and the resultant autohæmolysis is even more rapid than that of the congenital spherocytes.

REFERENCES

DACIE, J. V., MOLLISON, P. L., RICHARDSON, N., SELWYN, J. G., and SHAPIRO, L. (1953) *Quart. J. Med.*, N.S., **22**, 79.
EMERSON, C. P., SHEN, S. C., HAM, T. H., and CASTLE, W. B. (1947) *J. clin. Invest.*, **26**, 1180.
FLYNN, F., and MAIZELS, M. (1949) *J. Physiol.*, **110**, 301.
HAM, T. H., and CASTLE, W. B. (1940) *Proc. Amer. phil. Soc.*, **82**, 411.
MAIZELS, M. (1936) *Biochem. J.*, **30**, 821.
—— (1949) *J. Physiol.*, **108**, 247.
—— (1951) *J. Physiol.*, **112**, 59.
SELWYN, J. G., and DACIE, J. V. (1954) *Blood*, **9**, 414.
VANLAIR, C., and MASIUS (1871) *Bull. Acad. Méd. Belg.*, **5**, 3rd series, 515.
YOUNG, L. E., IZZO, M. J., and PLATZER, R. F. (1951) *Blood*, **6**, 1073.

Dr. T. A. J. Prankerd (The Medical Unit, University College Hospital Medical School, London):

Metabolism of the Red Cell in Congenital Hæmolytic Anæmia[1]

There is growing evidence that the viability of the human red cell is closely dependent on its metabolism so we have investigated the metabolism of normal red cells, and since most genetically determined diseases are manifestations of disordered metabolism we have also investigated the cells of congenital hæmolytic anæmia or hereditary spherocytosis (H.S.).

Some of the activities of the red cell are listed as follows: (1) Ion transport; (2) Methæmoglobin reduction; (3) Stromal lipid turnover; (4) ? maintenance of cell shape.

For the performance of these, energy is required and this is derived, ultimately, from the anaerobic breakdown of glucose. We have devised a method for studying the intermediary steps in this process, and particularly its relation to the regeneration of adenosine triphosphate, the immediate source of available energy within the cell (Prankerd and Altman, 1954).

[1] Based on a paper read before the American Society of Clinical Investigation—May 1954. This work is a result of collaboration with Drs. Lawrence Young and Kurt Altman of the University of Rochester, N.Y.

If whole blood is incubated with an inorganic radioactive phosphate salt at 37° C., there is an exchange of radioactive phosphorus between plasma and cells, the phosphorus being incorporated into esters within the cell. Using acid extracts of preparations from both hæmolysates and stroma these ester phosphates and inorganic phosphate can be separated by paper chromatography and estimates made of their relative specific activities.

In normal cells the pattern of phosphate turnover is reproducible. The exchange of radiophosphorus with respect to the plasma is a logarithmic function up to equilibrium and the relationships between intracellular fractions are such that 2,3-diphosphoglycerate is the most active except in the first hour. This compound bears a precursor relationship to adenosine triphosphate. Most of the compounds reach the same equilibrium after six hours and up to this time the activity of inorganic phosphate is less than that of either 2,3-diphosphoglycerate or adenosine triphosphate. In the stromal fractions the same compounds can be identified but their activities do not parallel those in the hæmolysate and therefore cannot result from contamination (Prankerd and Altman, 1954).

In cells from patients with hereditary spherocytosis examined similarly, a different sequence of events is found. In the hæmolysates the activity of 2,3-diphosphoglycerate is little changed, but no longer exceeds that of inorganic phosphate which is raised, whilst that of adenosine triphosphate is lowered. In the stromal fractions the activities of all compounds are very low. These features are summarized in Table I where the mean specific activities of adenosine triphosphate (ATP) and orthophosphate are shown with one standard deviation for a group of 18 H.S. cases.

TABLE I.—MEAN RELATIVE SPECIFIC ACTIVITIES AT FOUR HOURS IN HÆMOLYSATES

	ATP	Inorganic P
Normal cells	336 ± 21	348 ± 41
H.S. cells	221 ± 72	460 ± 132
Diff. of means ± S.E.	115 ± 18·3	112 ± 32·5

As long ago as 1938 Dische showed that red-cell hæmolysates would split adenosine liberating ribose 5-phosphate which was then converted to fructose 1,6-diphosphate. This can be utilized in glycolysis. We have incubated intact normal and H.S. cells with 0·05 M. adenosine. Normal cells show no change in phosphate partition in the first six hours but in 12 out of 18 cases of H.S. the abnormal relationships of the phosphate esters were restored towards normal. In the remaining six cases which constituted two families, the abnormality failed to show any response to adenosine. These abnormalities are unaffected by splenectomy.

This evidence suggests that in the red cells from patients with hereditary spherocytosis there are abnormalities of carbohydrate metabolism which are unaffected by splenectomy. One of these is characterized by a reduced capacity to phosphorylate adenosine diphosphate. This defect may be linked with the low potassium content of these cells observed by Maizels in 1936, since this cation activates the enzyme phosphoferase which catalyses the phosphorylation of adenosine diphosphate. The high orthophosphate activity might result from an enhanced activity of intracellular phosphatases.

The effect of adenosine in restoring towards normal the intracellular phosphate partition may be attributed to the conservation of adenosine triphosphate (ATP), since this is not required in the utilization of adenosine as it is with glucose. It appears that those cells which did not respond in the expected fashion may be lacking in their stroma the necessary enzyme which cleaves adenosine.

We have suggested elsewhere (Prankerd and Altman, 1954) that red-cell stroma may contain certain contractile elements which like myosin might have ATP-ase activity and be dependent upon continuous regeneration of ATP. The demonstration of ATP-ase in the red-cell stroma by Clarkson and Maizels (1952) supports this view. If this be so then the low activities of the esters from the stroma of H.S. cells may assume significance in relation to the spherocytosis.

A possible hypothesis interpreting their abnormalities with the clinical course of the disease is as follows:

The changes undergone by red cells during incubation at 37° C. for forty-eight hours have been reported by Selwyn and Dacie (1954). These changes demonstrate the greater susceptibility to hæmolysis of the H.S. cell with any depletion in the supply of metabolite for its use. The means by which various metabolites afford protection against hæmolysis is by enabling glycolysis to continue and the potential energy within the cell to be maintained. The channels through which this energy is ultimately directed are multiple and include the control of electrochemical ionic gradients, the turnover of lipids in the cell membrane, and possibly other functions, the failure of any of which will produce hæmolysis.

An analogy may be drawn between the changes occurring with *in vitro* incubation of H.S. cells and the effects of stagnation and hæmoconcentration in the spleen, as suggested in 194

by Ham and Castle. Selective trapping of H.S. cells in the spleen has been demonstrated by Young *et al.* (1951), and Gibson *et al.* (1946), and associates have shown that the hæmatocrit of splenic blood may be as high as 80%. Thus the supply of metabolite per cell will be reduced, and still further depleted by competition from the actively metabolizing lymphoid tissue of the splenic pulp. The H.S. cells trapped within the spleen will then be faced with relative starvation, a similar situation to that obtaining *in vitro*. After the splenic trap is removed, these cells may survive normally because of continuous access to plasma constituents, despite persistence of the metabolic and structural abnormalities.

REFERENCES

CLARKSON, E. M., and MAIZELS, M. (1952) *J. Physiol.*, **116**, 112.
DISCHE, Z. (1938) *Naturwissenschaften*, **26**, 252.
GIBSON, J. G., SELIGMAN, A., PEACOCK, W. E., AUB, J. C., FINE, J., and EVANS, R. D. (1946) *J. clin. Invest.*, **25**, 848.
HAM, T. H., and CASTLE, W. B. (1940) *Trans. Ass. Amer. Phycns*, **55**, 127.
MAIZELS, M. (1936) *Biochem. J.*, **30**, 821.
PRANKERD, T. A. J., and ALTMAN, K. I. (1954) *Biochem. J.*, **58**, 622.
SELWYN, J. G., and DACIE, J. V. (1954) *Blood*, **9**, 414.
YOUNG, L. E., PLATZER, F. R., ERVIN, D. M., and IZZO, M. J. (1951) *Blood*, **6**, 1099.

[*December* 14, 1954]

Experiment and Therapy in Hypertension

PRESIDENT'S ADDRESS

By Professor CLIFFORD WILSON, D.M., F.R.C.P.

THE linking together of experimental medicine with therapeutics as the special concern of our Section presupposes some connexion between the two. Nevertheless there is a point of view that this relationship is casual rather than functional and that the main advances in therapeutics have been based on empiricism rather than on the experimental study of the phenomena of disease. This is certainly true of the treatment of hypertension. Nothing could be more empirical than the devices which first the surgeons, and then the manufacturing chemists, have, in turn, provided for the relief of high blood pressure. It is, however, an axiom in therapeutics that the primary concern of the physician is not with the mode of action of a drug but with its effect on the natural history of the disease in the individual patient.

Yet I believe that in the search for further advances in treatment new problems have arisen which have brought therapeutics into closer relation with experimental medicine. This new alliance has been most productive in the treatment of metabolic disorders and of chronic diseases. The treatment of dehydration, the correction of electrolyte deficiencies, and the selective effects of radioactive isotopes are examples. In chronic disease the main problem has been the assessment of new forms of therapy. Here again the experimental method has been applied with great success in the planning of controlled therapeutic trials. This new form of investigation has made a valuable contribution to our knowledge of the natural history of disease; firstly by evolving methods for the quantitative analyses and assessment of prognosis, and secondly by applying these, not only in the treated but also in the untreated patient. Finally there are some diseases, such as hypertension, in which the experimental method has uncovered some of the specific mechanisms of the pathological process, thereby leading to a closer understanding of its natural history and to greater accuracy in diagnosis.

In selecting for my Address the subject Experiment and Therapy in Hypertension I had in mind some of these relationships between the experimental method and therapeutics. I do not intend to present any detailed results either of experimental investigations in hypertension or of the various forms of treatment now in vogue. At the present time, I think it is more appropriate to offer you some reflections on present-day therapy of hypertension from the points of view of its rationale, the basis of selection and assessment of cases, its effectiveness or otherwise, and the contribution which it may have made to our further understanding of the patients we are trying to treat.

DIAGNOSIS

One of the conditions which must be fulfilled before the results of treatment can be more satisfactorily assessed is greater accuracy in diagnosis. In the very numerous published reports, particularly on the surgical treatment of hypertension, most authors pay scant attention to diagnosis. Admittedly it can be a difficult problem, especially in patients with

early renal involvement, to decide between essential and renal hypertension and between the various causes of the latter. Unfortunately this is the group of patients in whom lowering of the blood pressure may be most urgently indicated. In carrying out sympathectomy the surgeon has a unique opportunity to make an accurate diagnosis of the pathological lesion, since renal biopsy can be easily and safely performed during the operation. I shall present a few observations we have made from examination of biopsy specimens in some 50 patients who have been treated by this operation. The rationale for treatment of high blood pressure can never be determined in the individual patient unless the primary diagnosis is fully understood. By this I mean not merely the placing of a label on a particular case, but, what is more important, taking into account the stage of the natural history at which treatment is commenced and recognizing the particular aspects of the pathological lesion which materially affect prognosis. I shall refer to those in detail when discussing assessment, but two examples will illustrate the argument. During the pre-war years an examination at the London Hospital of 56 cases of malignant essential hypertension, verified histologically, gave an average expectation of life of one year. At the present time, owing to the common practice of routine blood-pressure examinations for national service, life insurance and public employment, severe hypertension is being discovered with increasing frequency in young subjects and the development of features suggesting a transition to the malignant phase is being detected very early in the disorder. Our concept of the natural history of malignant essential hypertension therefore differs significantly from the one which was derived from pre-war studies. It follows that a comparison between a series of cases treated now, with untreated or differently treated cases described by other writers in previous years, may well be invalid. A second source of fallacy in therapeutic assessment is the grouping together of cases with the malignant type of hypertension, without clear evidence of the primary disorder. Now the natural prognosis is bad in malignant hypertension whatever the primary cause; but it is of first importance when selecting patients for treatment, no less than when assessing results, to know whether the kidney is relatively normal in structure as in the early cases of malignant essential hypertension, or whether it is grossly disorganized as in most cases of chronic nephritis.

In view of these considerations, I shall now discuss separately the different ætiological varieties of hypertension.

Essential Hypertension

Several operative procedures for the relief of essential hypertension have been employed in the last thirty years. Anterior rhizotomy was first used by Adson and the patients selected were said to be suffering from malignant hypertension. Since then various types of sympathetic resection have been carried out. It is very rare in the published reports to find any discussion of the specific reasons for operation. In general, the objective appears to have been lowering of the blood pressure, if possible to normal, in order to avoid complications in the heart, brain, retinæ or kidneys. Smithwick recently stated, however, that he no longer assesses his results on the fall in blood pressure produced but on statistical analysis of the survival period compared with patients treated medically. Such a criterion is of practical importance in a comparison of techniques, but it is of little value to the individual patient. There are I believe two principal reasons why active treatment may be considered necessary in essential hypertension, (1) the risk of chronic arterial degeneration (i.e. atheroma) leading to ischæmic heart disease, retinal lesions or cerebral vascular catastrophes, (2) the danger of malignant hypertension with its grave prognosis due to renal, cerebral, retinal and cardiac damage. There is a smaller group of patients who show no evidence of either of these distinct types of vascular complication, but who suffer from disabling symptoms, especially early morning or migrainous headaches, which appear to be a direct consequence of severe hypertension. Relief of these symptoms may be a proper aim of therapy.

Taking first the risk of chronic arterial degeneration and its sequelæ, hypertension is only one predisposing factor in the production of atheroma; there are several others—mechanical stress at focal points in the arterial system, the particulate state of circulating lipoids, obscure metabolic factors such as operate in diabetes, and probably hereditary predisposition. Yet in essential hypertension chronic arterial degeneration may not develop for ten, twenty or thirty years, during which period the patient may be free from symptoms. At what point in this long course should hypotensive therapy be applied and is it necessary for the blood pressure to be restored to normal? Since hypertension often returns to pre-operative levels after sympathectomy, is this form of treatment of any avail in preventing or reducing the development of severe atheroma? Should operation or drug therapy be withheld until signs of arterial disease appear? Atheroma may be focal in its incidence and irregular in distribution so that severe involvement of coronary or cerebral arteries may be present although all available investigations for arterial degeneration fail to reveal its presence. Moreover, once organic vascular damage has occurred in the heart or brain, sudden reduction

of the blood pressure level may do more harm than good. In the individual patient we have no method by which we can even approximately foreshadow the development or results of atheroma. In benign essential hypertension therefore the prevention of chronic arterial degeneration seems to be an inadequate reason for employing such a drastic and uncertain form of treatment as sympathectomy. Nevertheless I think the questions I have asked need to be studied. There is no doubt that high blood pressure predisposes to obliterative arterial disease and its consequences, and the expectation of life is thereby shortened. It is possible that a large-scale investigation in which clinicians, morbid anatomists and biochemists took part, might demonstrate that modification of hypertension by drug treatment reduces the hazards of atheroma. Such an investigation would have to be planned and controlled on the same lines as therapeutic trials of antibiotics in chronic infectious disease. Here is a field in which the experimental method might be appropriately applied to a therapeutic problem which is rapidly increasing in size and in urgency.

The other indication—the risk of malignant hypertension—is in a different category and it is at this point that the study of experimental hypertension may help us to understand the nature of the problem more clearly. In the first place we have convincing evidence that hypertension—independent of any metabolic abnormality—is the prime factor in producing the acute arteriolar necroses which are the most serious consequence of malignant hypertension. Secondly there is strong presumptive evidence from the recent work of Byrom that in malignant hypertension the arterioles of the brain, and probably of the splanchnic area, may pass into a state of excessive focal vasoconstriction. Such focal vasoconstriction or its consequences may well be the basic disturbance which is responsible for acute hypertensive retinopathy, encephalopathy, pulmonary œdema and renal arteriolar necrosis. Thirdly, in animal experiments, both arteriolar necrosis and focal spasm can be halted or prevented by lowering the blood pressure. Fourthly, if malignant hypertension persists, extensive renal vascular damage may set in motion a vicious circle which maintains the hypertension and renders the process irreversible. These considerations provide clear indications for the prompt relief of hypertension. The essential requirement is to produce an effective lowering of blood pressure before irreversible changes are produced in the kidneys. This objective poses two further questions: first, what is an effective lowering of the blood pressure? I think the answer is as close an approximation to normal as possible, for restoration to normal is rarely practicable and perhaps unnecessary. If papillœdema regresses and further renal damage is prevented treatment is well justified, but unless an appreciable fall in blood pressure is maintained, the ultimate prognosis remains poor, for the reversibility of malignant essential hypertension is far more difficult and uncertain than the reversal of the malignant renal hypertension which may follow removal of a single diseased kidney.

The second question is, can the development of the malignant phase be anticipated? The diagnostic sign of malignant hypertension is papillœdema, and it is not possible in the absence of this sign to forecast with certainty the transition to the malignant phase. In certain cases of severe benign hypertension the imminence of this transition is sometimes suspected. For example, the development of severe headache associated with a fixed diastolic pressure, over 130 mm., in a young male subject is an ominous sign, and if the diastolic pressure is rising it is even more so. The appearance of retinal hæmorrhages with or without exudates, or the occurrence of an isolated attack of encephalopathy, characterized for example by severe frontal headache, a convulsion, loss of consciousness or transient paresis—all these suggest a qualitative change in the character of the peripheral vascular disorder from the benign to the malignant type.

It is in this group that sympathectomy and hypotensive drug therapy are often most effective in lowering the blood pressure and relieving symptoms. Far more attention should be paid to the natural prognosis and the renal histological changes in these patients. Most of them show retinopathy in the form of retinal hæmorrhages which may be associated with exudates but without papillœdema. I should like to refer here to a common practice, especially in the United States, of grading hypertension according to the severity of lesions in the retina. The patients I have just described are graded as Group III. If retinal hæmorrhages are close to the disc there is often some degree of papillœdema and presumably the hypertension is then graded as Group IV. However, such papillœdema does not necessarily indicate malignant hypertension. It is almost invariably unilateral and subsides as the retinal lesions regress. This grading of high blood pressure is useful in emphasizing the importance of retinal lesions, but it neglects, and I think this is most serious, the variations in course and prognosis which the patients in this transitional group exhibit. The hallmark of a good classification is that its subgroups are homogeneous. There is evidence that a proportion of patients with so-called Grade III hypertension develop the malignant change but we have insufficient information to say what proportion; there are others, however, (particularly women) who continue for many years, with or without recurrence of the above

symptoms, and we cannot be certain that papillœdema or renal involvement will ultimately appear. It is probably justifiable to attempt to lower the blood pressure in these patients by surgical or medical means; what is unjustifiable is to regard them as examples of malignant hypertension or even as a homogeneous group in assessing the value of a particular form of therapy. Fig. 1 illustrates the clinical course in a patient of this type. She presented at the

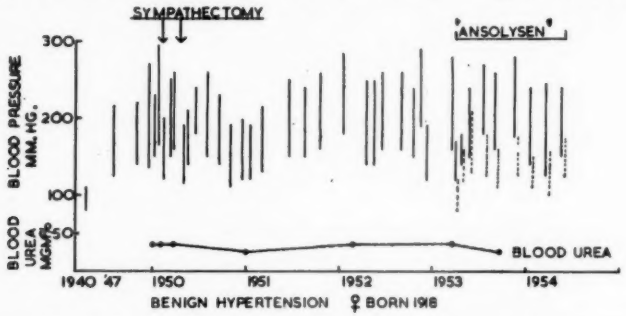


FIG. 1.—Showing the effect of sympathectomy and subsequent hypotensive drug therapy on a patient with severe benign hypertension.

age of 32 with a very high blood pressure, severe headaches and retinal hæmorrhages. Bilateral lumbo-dorsal sympathectomy produced a temporary fall in blood pressure with relief of symptoms but two years later the blood pressure had returned to pre-operative levels and has continued there for three years without any evidence of transition to the malignant phase. No papillœdema or clinical evidence of renal involvement has been observed at any stage yet histological examination of renal biopsy material taken at the time of operation shows the characteristic glomerular and arteriolar necroses of malignant hypertension (Fig. 2). Whilst it could be argued that in this patient sympathectomy and

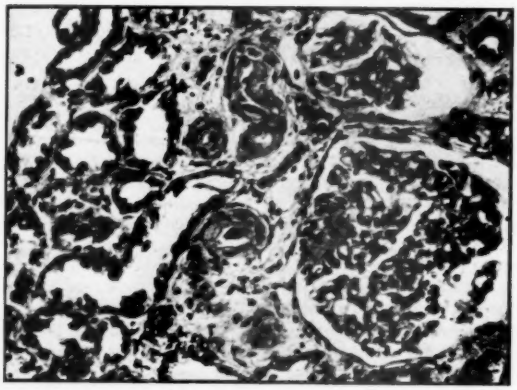


FIG. 2.—Organized necrotizing arteriolitis in a renal biopsy section taken at the time of sympathectomy in the same case as Fig. 1. ×184.

later the administration of hypotensive drugs had prevented the transition from the benign to the malignant phase, a similar protracted course is not infrequently observed in other patients of this type who have had no hypotensive therapy.

I come now to those patients in whom the diagnosis of malignant essential hypertension is unequivocally established by the finding of bilateral papillœdema. In assessing the results of treatment, attention is naturally focused on the reversal of papillœdema and the absence of progressive vascular damage as evidenced by improvement in albuminuria and renal function, or at any rate no further deterioration. It is important to realize that activity, in the sense of production of arteriolar necrosis, is not continuous in malignant hypertension. It is more often phasic and may possibly in some cases be confined to a

single episode. Histological examination of the kidney quite commonly reveals only organized lesions of the renal arterioles and glomeruli, without evidence of recent acute arteriolar necrosis. It was this observation which led Fahr to describe endarteritis rather than necrotizing arteriolitis as the diagnostic lesion of malignant nephrosclerosis. Examination of renal biopsy sections from *early* cases of malignant hypertension more often shows healed than acute vascular changes, i.e. in these patients operation has been performed during a quiescent period after an acute hypertensive episode.

The clinical findings in this inactive stage show the same freedom from acute disturbances. Most characteristic are the optic fundi. The discs, though indistinct at the margins and still showing lack of definition of the optic cups, reveal no measurable papillœdema and new hæmorrhages and exudates are not observed. This appearance is sometimes called chronic papillœdema or secondary optic atrophy. It is better regarded as a sign of quiescence of the specific focal vasoconstriction which characterises malignant hypertension. In selecting patients for operation, or in assessing prognosis and response to treatment, awareness of this phasic character of the disease and recognition of the active and quiescent states appear to be of considerable importance.

As a result of combined clinical, histological and experimental observations we have reached a much clearer understanding of the condition which Allbutt sixty years ago called hyperpiesia. Allbutt separated this condition from renal hypertension, because clinical evidence of renal involvement was not observed during the whole course of the disease. We now have convincing evidence that severe "hyperpiesia" may lead to involvement of the kidneys—and other organs—by the production of necrotizing vascular lesions, and clinically we recognize this malignant phase of the disease by the appearance of papillœdema. Just as nephrosclerosis is now accepted as the late irreversible stage of renal damage in this malignant phase I would suggest that papillœdema is a sign, in the great majority of untreated cases, of an irreversible functional stage. Both these late manifestations may be preceded by hypertensive crises in which transient symptoms of malignant hypertension may occur and focal vascular necrosis may be produced. Whether or not this phasic disorder passes into the irreversible stage of malignant nephrosclerosis depends on factors we do not fully understand, but this sequence is by no means inevitable; in support of this is the occasional finding of healed acute hypertensive lesions in the glomeruli and renal arterioles in patients who have followed a typical clinical course of benign hypertension.

There is still a place for sympathectomy in early malignant hypertension. The response to hypotensive drugs may be poor, side-effects may be incapacitating, the patient may not co-operate sufficiently to persevere with drug treatment or the necessary supervision may not be available. When, however, more than a slight degree of nitrogen retention is present and concentration tests are impaired, or when a previous cardiac infarction or cerebral hæmorrhage makes the surgical risk unjustifiable, treatment with drugs of the hexamethonium group is of undoubted value. Severe headaches may be relieved and vision improved; attacks of encephalopathy often respond dramatically within a few hours and cardiac asthma may subside. Our observations on renal function during the course of drug treatment are still rather scanty but so far we have obtained no evidence either of improvement or of sudden deterioration that could be attributed to the treatment. The same conclusions were reached about the influence of sympathectomy on renal function in the early days of treatment. Patients with malignant hypertension subjected to bilateral sympathectomy showed no significant improvement in renal function apart from possible reversal of extra-renal nitrogen retention. It appears then that impairment of renal function in malignant hypertension is in the main due to irreversible organic changes; and furthermore if the blood pressure level is subsequently lowered, internal regulating mechanisms in the surviving renal tissue are capable of maintaining function relatively unchanged.

Chronic Nephritis

The indications for treatment and the form of therapy to be employed in chronic nephritis are in my view rather different from the foregoing. This conclusion is based on two considerations; first, that structural renal damage is always severe in chronic nephritis, and second that once the blood pressure has reached a high level, e.g. 200 mm. systolic, the malignant change develops much more frequently than in essential hypertension. Many years ago, Dr. Kimmelstiel and I found that in a post-mortem series of 250 consecutive cases of essential hypertension less than 5% presented the histological features of malignant hypertension. If the estimate were confined to the younger age groups covering the main incidence of chronic nephritis it is possible that this figure might be somewhat higher, possibly double; but it would not approach the incidence of terminal malignant hypertension in chronic nephritis, which is over 50%. The figure is approximately the same for both Type I and Type II nephritis. It is interesting also that this is roughly the incidence of malignant hypertensive lesions in rats with experimental renal hypertension. I feel therefore

that when the blood pressure rises towards the 200 mark in chronic nephritis, whether retinopathy is present or not, an attempt should be made to reduce the level. It might be questioned whether reduction of blood pressure is justified in chronic nephritis to the same extent as in essential hypertension. One can only say there is no evidence either that a high blood pressure is beneficial in chronic nephritis or that lowering the pressure to a more moderate figure causes further impairment of renal function. There is, on the other hand, both clinical and histological evidence, especially in chronic Type I nephritis, that progressive renal damage follows the development of a high blood pressure. This "hypertensive transformation" is a very characteristic feature of chronic nephritis. It may occur over a relatively short period of six months or so following many years of fairly stable, slight to moderate, hypertension. Why this phenomenon should occur is not clear. There is no evidence at this stage of exacerbation of the nephritis such as may occasionally be accountable for hypertensive crises early in the disease. This is confirmed by the failure to find fresh lesions of glomerulo-nephritis on histological examination. It seems more probable that gradually increasing ischæmic damage in glomeruli and arterioles, possibly hastened by advancing age, eventually oversteps the threshold at which progressive hypertension develops. Whatever the explanation, this phenomenon is usually associated with rapid deterioration in renal function. Following this, there is then a considerable likelihood that, usually within a year in men and rather longer in women, the hypertension will enter its malignant phase, with clinical features differing from malignant essential hypertension only in the greater prominence of uræmic symptoms. If this rising blood pressure is detected in time, i.e. before renal impairment is advanced, and the level can be reduced, I believe the downhill course may be retarded if not arrested, and the expectation of life may be considerably prolonged (Fig. 3). In the past a number of these patients were subjected to sympathectomy. There were a few successes, but more failures, since the operative risk is considerable owing to the severity of structural renal damage. Blood pressure lowering drugs offer a more satisfactory form of treatment and even when the signs of malignant hypertension have developed, some of our patients with chronic nephritis have experienced symptomatic relief from headaches, myocardial failure, hypertensive encephalopathy and retinopathy.

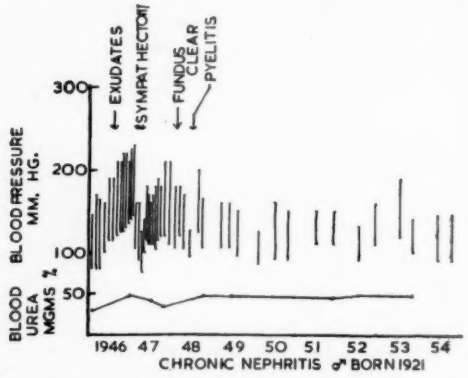


FIG. 3.—Gradual rise in blood pressure in chronic Type I nephritis checked by sympathectomy with no further deterioration in renal function over seven years.

I feel less sanguine about the value of hypotensive treatment in chronic Type II nephritis. The malignant termination is if anything more common in this condition than in Type I. Whilst symptomatic improvement at this stage may be expected from hypotensive drugs I doubt whether their use at an earlier stage has in any of our patients increased the expectation of life. This is what might be anticipated from a study of the renal lesion, which is invariably a diffuse progressive glomerulo-nephritis. Even after a malignant termination it is unusual to find on microscopic examination secondary hypertensive changes in the kidneys, i.e. in this form of nephritis it seems unlikely that hypertension, even of the malignant type, is responsible for any appreciable degree of structural renal damage. It may, of course, produce fatal vascular lesions in other organs but this is not common.

It is necessary to mention at this point that malignant episodes of hypertension occasionally undergo spontaneous reversal in chronic nephritis. Such episodes have been observed in two circumstances. Firstly in chronic nephritis complicated by pregnancy. These patients may develop papillœdema and eclamptic fits towards the end of pregnancy or more rarely in the puerperium. The condition is often wrongly diagnosed as pregnancy toxæmia, the pre-existing renal lesion being unrecognized. Spontaneous resolution of papillœdema and improvement in renal function is not infrequent after delivery but the blood pressure may continue at a high level. A similar sequence of events is occasionally seen in the early stages of chronic Type II nephritis. In these patients there is usually clear-cut evidence of an exacerbation of the nephritis with increase in œdema, some degree of hæmaturia and deterioration in renal function. As the exacerbation subsides a coincident reversion from

the malignant to the benign type of hypertension may occur. These features in the natural history of nephritis must obviously be taken into account when hypotensive treatment is contemplated or the results are being assessed.

Bilateral Pyelonephritis and Hydronephrosis

These conditions are not usually accompanied by a degree of hypertension which requires specific treatment. Nevertheless we have in our records a number of patients in whom severe hypertension, occasionally progressing to the malignant stage, has been apparently caused by one or other or a combination of both these processes. In 3 cases, all children, the advanced degree of hydronephrosis seemed to indicate a congenital maldevelopment. A period of improvement, with reversal of the malignant hypertension, has followed sympathectomy. It is essential in such cases that the possibility of a local obstructive cause should be looked for and if found, corrected. In view of the considerable reduction in renal tissue and associated infection in hydronephrosis, drug treatment rather than sympathectomy is at present to be preferred.

One point which has emerged from our study of renal biopsy sections after sympathectomy is the occasional impossibility in detecting chronic pyelonephritis without histological examination. In one case renal biopsy showed bilateral pyelonephritis without contraction, although full investigation had revealed no abnormality in the urine, renal function or intravenous pyelogram. It seems inevitable therefore that in the selection of patients with essential hypertension or chronic nephritis for hypotensive drug treatment there is a definite risk that a few cases of chronic pyelonephritis will be included in error.

Unilateral Renal Disease

The occurrence and natural history of hypertension in unilateral renal disease is particularly relevant since it presents a striking parallel with experimental hypertension in animals—especially in the rat. This parallel can be extended even more remarkably to the therapeutic response, since removal of the abnormal kidney abolishes hypertension in only about 50% of cases—a similar proportion to that which obtains after unilateral nephrectomy in hypertensive rats. There is now convincing proof from our original and from more recent experiments that persistent hypertension in the rat after removal of the clamped kidney is attributable to secondary hypertensive damage in the opposite kidney. Similar hypertensive changes are commonly observed in the contralateral kidney in man, and it seems a fair presumption that they account for the fact that in some cases the hypertension is not abolished after nephrectomy, and in others may even rise to a higher level than before operation. It is therefore a wise precaution before nephrectomy to make certain by ureteric catheterization that urine from the contralateral kidney shows no evidence of active renal damage.

The reversal by nephrectomy of malignant hypertension in unilateral renal disease is one of the most satisfying and dramatic results of treatment. Nevertheless it should not be assumed that other forms of malignant hypertension are similarly reversible. Two conditions are necessary to abolish malignant hypertension: (1) the primary cause of the hypertension must be removed, and (2) secondary hypertensive renal damage must not have passed a certain critical stage. In the common forms of malignant hypertension, i.e. complicating essential hypertension or chronic nephritis, the cause of the hypertension cannot be removed and, except in the very early stages, secondary hypertensive renal damage is always severe. All one can expect in treating these conditions is to neutralize in part the intense vasoconstriction of malignant hypertension by superimposing a physiologically different vasodilator effect. But the cause of the malignant hypertension remains; I have seen a patient with essential hypertension develop papillœdema on three occasions, the first time before operation and the second and third times during relapse after successive sympathectomies of increasing extent. This thesis is aptly illustrated in the rare type of hypertension due to phæochromocytoma of the adrenal. Paroxysmal hypertension due to this tumour, after a variable interval, tends to become permanent and may pass into the malignant stage. The early paroxysmal hypertension is relieved by removal of the tumour but the later fixed hypertension usually persists after operation. In these patients, even though the primary cause of the hypertension is removed, the condition may be rendered irreversible by the development of secondary hypertensive lesions in the kidneys.

The Adrenal Cortex and Hypertension

In conclusion, it is difficult to avoid some comment on the relationship between the adrenal cortex and hypertension. I am aware that there are many causes of high blood pressure and that the body has a limited choice of functional and structural responses to a wide variety of environmental hazards. Nevertheless, ever since I observed, some twenty years ago, the features of benign and malignant essential hypertension reproduced in patients with Cushing's

syndrome I have wondered whether the common forms of high blood pressure might not have some endocrine basis; this impression was strengthened when it became apparent that Cushing's syndrome could arise in the absence of any apparent structural abnormality in the adrenal cortex. Before entering this speculative field I must emphasize that at present there is no evidence that in man the adrenal cortex secretes a hormone which causes either essential or renal hypertension. In the rat, the hypertension which follows either renal artery constriction or total nephrectomy is abolished if the adrenals are removed. Whether this adrenal factor independently maintains a background of arteriolar tone on which other forms of vasoconstriction are superimposed, or alternatively whether the kidney directly influences this adrenal mechanism is a vital but as yet an undecided problem. Such evidence as we have points to the latter, i.e. that the normal kidney in some way inactivates a pressor factor derived from the adrenal cortex. Moreover the evidence suggests that the excess of this pressor factor in experimental renal hypertension is not due to its over-production by the adrenal cortex but to failure of the kidney to deal with the *normal* cortical output. Since deoxycortone acetate or even increased salt intake can act as effective substitutes for the adrenal cortex in these experiments it seems likely that the adrenal pressor factor acts through some influence on tissue electrolyte distribution. There is a possible relevance here to the effect of sodium restriction on hypertension in man, and the variable reponse to this form of therapy may be attributable to the influence of the intact adrenal glands. Thus in rats variations in salt intake have little effect on renal hypertension when the adrenals remain intact.

These experimental findings obviously provide no rational basis for adrenalectomy in the treatment of human hypertension. If indeed renal or essential hypertension in man were due to the same mechanism as experimental hypertension in the rat, removal of the adrenals would not improve the situation, since, in order to keep the patient alive, substitution therapy would, of necessity, restore the normal supply of adrenal pressor factor without correcting the abnormality of its regulation. This is indeed what appears to happen for, from reports in the literature, it seems that when patients with essential or renal hypertension are submitted to total adrenalectomy it is subsequently very difficult to prevent cortical insufficiency without elevating the blood pressure. Moreover in these adrenalectomized subjects physiological doses of cortisone are sufficient to restore hypertension, which supports the view that over-action of the adrenal pressor mechanism is not involved (Fig. 4). The situation is quite

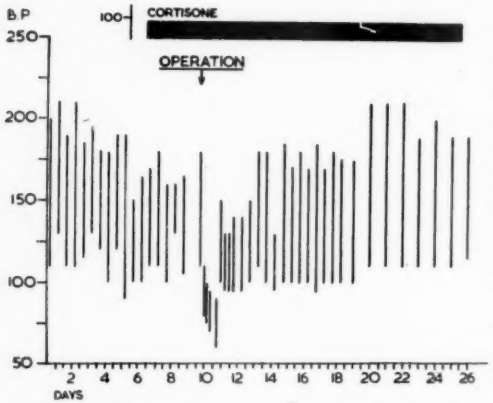


FIG. 4.—Total adrenalectomy for carcinomatosis in a patient with benign hypertension. Hypertension persists after operation on a relatively small dose of cortisone.

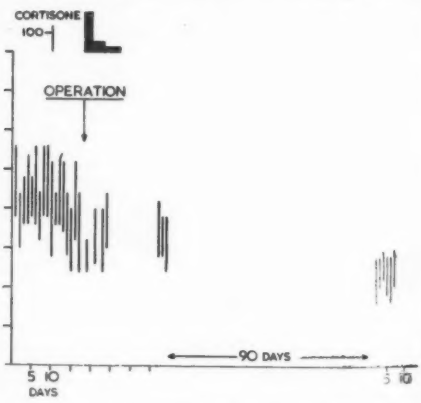


FIG. 5.—Subtotal adrenalectomy in a patient with Cushing's syndrome restores blood pressure to normal.

different in those patients whose hypertension is associated with Cushing's syndrome. Here, removal of an adrenal tumour or subtotal adrenalectomy will cause prompt reversal of Cushing's syndrome and a return to the eucortical state without recurrence of the hypertension (Fig. 5).

I think it is along these lines that future developments may take place. Here and there surgeons are performing the operation of total adrenalectomy for various reasons. Whilst this practice may not commend itself entirely to us in the realm of therapeutics it does offer a remarkable opportunity for our more rational activities in the sphere of experimental medicine.

Section of General Practice

President—R. J. MINNITT, M.D., F.F.A. R.C.S., F.R.C.O.G.

[*October* 20, 1954]

General Practice in Review

VALEDICTORY ADDRESS

By A. TALBOT ROGERS, M.B., B.S.

SEVERAL years ago, at a time when on all sides one was hearing that the status and scope of general practice was falling, and that soon no youngster of talent or ambition would ever look to general practice for a career, I was talking to the Secretary of the Nuffield Trust, and he remarked on how little was really and authentically known to laymen like himself of the true pattern of life of the general practitioner.

He felt it was time someone wrote what he called "a philosophy of general practice", which, while in no way ignoring the trials and frustrations of general practice, would also bring out its satisfactions and rewards. What is it, he asked, that makes general practice so satisfying a life to so many of you family doctors? Tell us that and we will be well on the way to preserving what is best in practice, and to attracting worthy recruits to this branch of the profession.

Now this seemed to me a good idea, and when, some months later, I found myself with time on my hands, I sat down and tried to rough out a philosophy of general practice. But it came to nothing, for I found, try as I might, that what was coming from my pen might possibly be called the philosophy of a general practitioner, but by no stretch of the imagination was it a philosophy of general practice. It emerged as *my* account of what mattered most to *me* in *my* life in *my* practice, and could certainly not be claimed to have any general application to countless other practitioners working in their own separate ways against their vastly differing practice backgrounds. Little had been written then about general practice. Much has been written since, but nothing that I have read has done anything but confirm for me the conclusion that I then reached that there can be no single philosophy of general practice. In general practice we are all individuals, conducting our practices in our own individual ways, working directly with our patients, and adapting our methods to their needs. This remains true whether we are working alone or in groups, and I hope we may ever preserve this individuality, even while we strive to adapt, and absorb the modern advances in medicine, and in technicology.

But though there may be forthcoming no philosophy of general practice, that does not mean there can be no general practitioner philosophers. The short history of this youngest Section of the Royal Society of Medicine can already give the lie to such an idea. So far we have had four Presidential Addresses, if one includes the Inaugural Address given to the first meeting of the Section by Dr. Geoffrey Barber, then our Senior Secretary. Each of these four Addresses has reflected a different facet of general practice, which each of us could recognize as part of general practice as we knew it, and yet in no way revealing the whole varying pattern. Even Dr. Barber, who set out bravely to answer the question "What is General Practice?" would be the first to admit that his answers to his own question might well have received different emphasis had his professional life been cast not in Dunmow but in Darlington. Certainly Dr. E. P. Scott's well-remembered and entertaining talk on the changing pattern of Metropolitan Medicine could not have been written by anyone practising far outside the square mile in which we now meet. Dr. G. F. Abercrombie revealed the thoughtful contribution that a keen and able general practitioner obstetrician could bring to this branch of practice, and the consistently good results such a practitioner could achieve. With Dr. J. D. Simpson we were back in imagination at our University remembering acutely the physical and psychological problems of adolescence, and regretting only that we did not always have so understanding and so sensible a confidant in our generation as Cambridge has in Dr. Simpson.

During the past five years, on what I might call the academic side of general practice, much thought has been taken, much planning pursued, and prominent in this planning have been many who are members of my audience to-night. The result has been the achievement of this flourishing Section of the Royal Society of Medicine, and the unexpectedly easy birth and rapid growth of the College of General Practitioners.

One of the objects which this Section and the College have in common with the organized professional bodies is the improvement of the status of the general practitioner. Whether we seek to secure this by influencing his undergraduate and postgraduate training, by encouraging him in research, by enabling him to exchange ideas with colleagues, to have ready access to hospital, or, more mundanely, by listening to and trying to allay his dissatisfactions by negotiating a concession here, or preserving a privilege there, we are all concerned with understanding practice as it exists, and with devising means by which it may be improved. That is why we have all read with interest the several reports on general practice published in recent years, and that is why I thought it might be opportune to discuss some of the points raised in these reviews which have influenced my own thinking.

There are four reviews we should consider—those of Collings, Hadfield, Taylor and the Central Health Services Council. It so happens that I saw something of the preparation of all four reports. I met Collings when he was first in England preparing his data, and I was sometime a member of each of the Steering Committees guiding the other three reports. Collings, a young Australian doctor, with something of the crusader, almost of the evangelist, in his make-up, came to England to study conditions of general practice here after having practised for a while in Australia and New Zealand. His travels led him to rural, to urban-residential and to industrial areas. He seemed, on the whole, not dissatisfied with rural general practice, but some of the practices he found in the industrial areas shocked him profoundly. His reactions may be summed up in his own words: "My observations have led me to write what is indeed a condemnation of general practice in its present form: but they have also led me to recognize the importance of general practice. . . Instead of continuing a policy of compensating for its deficiencies, we should admit them honestly and try to correct them at their source." He pointed out how easy it was for a man coming from his teaching hospital with sound scientific discipline quickly to slip into inadequate habits of perfunctory examination and limited treatment if he were compelled to work with undue hurry and inadequate help in unsatisfactory surroundings. He deplored the lack of planning for good general practice and sought to incite general practitioners into planning the future for themselves—a future in which Collings thought that group practice units of six or more doctors working together from State-provided—or at least State-subsidized—premises, and employing their own staff of secretaries, nurses and technicians, would play a large part.

It must be confessed that the general practitioners did not rally to this call from Collings. In the main, Collings had a bad press. It was pointed out that he had visited few practices, and though he may have seen some bad ones, they were in no way characteristic of practice even in the least favoured industrial areas. For him to generalize from them and condemn general practice outright was carrying the zeal of the reformer too far. But though little seemed to happen as an immediate consequence of the publication of his report, there is no doubt in my mind that Collings' labours were not wasted. His reconnaissance stirred the conscience of the profession, and much that has happened since in general practice has stemmed from its publication. But for Collings, it is unlikely that the next enquiry—that made by Hadfield—would have been undertaken so soon.

Launched by the British Medical Association and conducted by one of their assistant secretaries, this review set out to avoid the criticisms levelled at the Collings enquiry. A much larger number of practices were visited, they were chosen completely at random, and an attempt was made to check the findings of Dr. Hadfield (who conducted in person the field survey) by comparing his report with postal answers to questions similar to those that he would be posing but sent to the thousands of other doctors who could not be visited. Dr. Hadfield went about his onerous task with diligent persistence, travelling to all parts of the country, asking his questions, making his observations, drawing his conclusions, and eventually writing his field survey and fighting long and successfully to publish that survey as his own objective and subjective findings without it being edited, where discrepancies arose, to match the postal enquiry, or his Steering Committee's conclusions and recommendations. He studiously avoided deserving to be the target of the taunt that Adlai Stevenson cynically levelled at one of his opponents whom he declared ended a speech by saying "These are the conclusions on which I base my facts".

The Hadfield Report did, I believe, what it set out to do; it produced a description of a randomly chosen cross-section of general practice in 1951–52. It put in perspective the good and the bad. It will remain for all time the most valuable source of data on the methods of practice current at the time of its compilation, and the availability then for the practitioner of professional and ancillary help. No such authoritative information had ever before been compiled. Many of the conclusions drawn and recommendations made by the Committee have already had their effect in shaping the future policy of the British Medical Association. The Association believed that the report unquestionably showed that unsatisfactory practices were far fewer than Dr. Collings had suggested. But Dr. Collings was unrepentant. Commenting on the Hadfield Report in the *Medical World* he suggested

that Dr. Hadfield had set his sights too low and that, had he demanded higher standards, his conclusions as to the proportion of inadequate practices would have tallied much more closely with Collings' own.

Simultaneously with Dr. Hadfield, Dr. Stephen Taylor had been carrying out his own field survey on behalf of the Nuffield Provincial Hospitals Trust. But his approach and his methods were different. He deliberately sought out practices of good repute, to analyse their buildings, their equipment and their methods of practice, and to publicize those aspects thought worthy of imitation or adaptation in other practices. Dr. Taylor had had no previous first-hand experience of general practice. He brought to his task a vast energy, an acute observation from which nothing could be hidden, and a boundless childlike enthusiasm. Never before had the medical profession greater need to heed the warning of Rabbie Burns "A chield's amang you taking notes, And, faith, he'll prent it." Words flowed in fascinating procession from his pen. In the end, the Nuffield Trust published a large and handsome volume that contained perhaps an eighth of what Dr. Taylor had written, but, I hasten to add, an eighth so well selected as amply to deploy all the cogent ideas and arguments Dr. Taylor's odyssey had evoked. No longer can the Secretary of the Nuffield Trust complain of lack of information about the stuff that general practice is made of. Nor need the young aspirant to general practice, armed with Taylor's book, be starved of ideas for helping him to establish his own preferred pattern of practice.

Lastly has come the report of the Committee on General Practice of the Central Health Services Council. Its recently published conclusions and recommendations are still to be the subject of discussion and negotiation between the profession and the Government: some are undoubtedly controversial; for both these reasons it would be inappropriate for me to enlarge upon the report. It is sufficient for our purpose to note that this Committee contained lay members as well as medical, heard a multitude of views from lay and medical individuals and organizations, and ended by producing a report that can in no way be called revolutionary. Largely it accepts the pattern and predicts the evolution of present-day practice along lines that depart little from tradition.

I feel that these reviews have revealed very little that was new. Having so much material to survey and select, one naturally chooses to high-light those portions of the reviews that most closely correspond to one's own favourite theses.

But before I begin quoting from my texts, let me first state for myself what it is general practice holds that makes it satisfying to me. I think it is the opportunity it gives for doing things in my own way for my own patients, and going on doing so, not at one special time, but through all their lives, in all their illnesses and tribulations, getting to know them and their families, their homes, their jobs, and their habits—in fact, being their family doctor. I want to do as much as I can for them myself, but I realize that to do so I need a variety of help, help which can extend my usefulness to them. Finally, when they are beyond help, I still want to offer what solace I may to them and to those who care for them.

When I come to analyse my *Credo* I find that *First*—The privilege of "doing things in my own way" carries with it a high measure of responsibility. If I, and I alone, am to decide what care is best for my patient, my standards must be high, my sense of responsibility must be dominant. Geoffrey Barber in his Inaugural Address talked of this responsibility as an ideal, saying: "It is the responsibility for a patient, even sometimes against his will; a responsibility both for him and his family, in health and in sickness from birth to death. The kind of responsibility which makes one accept the night-call, the blizzards, the farm-tracks, the slums, because the visit of the family doctor is the one thing which is going to relieve what appears to be a hopeless situation." No one, I believe, is fitted for general practice who is unwilling to accept this responsibility.

Second.—"For my own patients." I like feeling that certain patients would always prefer to have my care and my advice. But no doctor can be always available, or should attempt to be; as Stephen Taylor says: "Occasionally a doctor will push the doctrine of continuity of care to absurd limits. He comes to believe that nobody but himself can ever look after his own patients. In his megalomanic paranoia he refuses to take holidays or time off for sickness. So over the years the quality of the medical care he gives tragically deteriorates." Fortunately this attitude is rare, and most of us make deputizing arrangements by partnership or rota schemes. My partners and I prefer to do this within our partnership, and try to see to it that while retaining the "patients of our own" as far as is possible, we still try to let each patient know well more than one of the partners. Hadfield has some interesting paragraphs showing the extent to which sharing of patients varies in different practices. Both he and Taylor seem to believe that the pooling of patients interferes seriously with any continuity of observation and understanding of patients. On the other hand, nothing can be more destructive of true partnership than a jealous guarding of patients from all contact with one's partners.

Third.—"Not at one special time but through all their lives." Surely this is the whole essence of general practice. Again, I quote Stephen Taylor. "If there is a single unmistakable characteristic of general practice it is to be found in the continuing observation of the patient from month to month, from year to year, and from illness to illness." It is also the reason why the methods of general practice are not, and cannot be, those of the consultant clinic. The knowledge general practice gives of past history, the opportunities it provides for observing the effects of an illness on an individual and his family, for following up the sequelæ of illnesses, and noting the ultimate efficacy of treatment are as unique as they are fascinating.

Fourth.—"Not for one special ailment but in all their illnesses and tribulations." This, too, is to me one of the excitements of general practice: the challenge of never knowing what call will next be made upon one; the need to be ever vigilant for that small departure from the normal, that small change in habit, of gait or of appearance that may be the first but vital clue to something serious. All these are a constant stimulus. I have included tribulations as well as illnesses, for, to-day, the general practitioner has not infrequently to offer social and even spiritual care to his patient. Part worldly-adviser, part social provider, part father-confessor, his role is complex but inescapable.

Fifth.—"Getting to know them, and their families, their homes and their job, their habits and their fads—in fact, being their family doctor." No-one can claim to be a family doctor who has not absorbed just this information about the environment that is shaping the lives of his patients. And no other doctor has our opportunity in this sphere. Here again is Stephen Taylor speaking: "The G.P. can claim that his relation to his patient's homes is virtually unique. He is the only doctor to see his patients at home whenever necessary. This enables him to have a special insight into home environment, physical and emotional; such insight is important both in planning treatment and in assessing causation and prognosis." I believe that it is in instilling, and in demonstrating, the importance of these factors that the G.P. can make his chief contribution to undergraduate, or early postgraduate, medical education, and I am glad to observe the increasing opportunities he has to do so.

Sixth.—"To do as much as I can myself." It is what the doctor can do himself, particularly in the crises of life, that forges the strongest bonds between him and his patients. By this I mean that he should undertake to the full all the tasks that come within the scope of the average well-trained general practitioner. In some areas it is all too easy to unload all manner of duties upon hospitals or clinics, and in so far as a doctor habitually does this, his value to his patient, the esteem in which he is held, and the satisfaction he himself gains from his practice, all inevitably fall. Herein I believe is one of the reasons for the existence of conditions about which Collings was impelled to write: "General practice is now worst in close proximity to large hospital and clinical centres, and improves in both scope and quality almost in proportion to the distance away from these centres. Rural practice represents the last outpost of real family doctoring, and in some respects it has gained more from modern medical knowledge and techniques than urban practice."

Seventh.—". . . I need a variety of help—help which can extend my usefulness." Part of this help needs to be provided inside the practice and Taylor particularly has much to say on the proper deployment in the practice of ancillary staff. But the general practitioner also needs frequent help for his patient from other sections of the health service, and here more than anywhere else the analyses of field enquiries and of evidence taken in the several surveys will prove most helpful. Hadfield places foremost among his adverse impressions of practice in 1951 a lack of cohesion in the service and in the medical profession. He remarks that: "The general practitioner, the consultant, and the public health medical officer need to get to know each other and then to learn to work in concert. There is growing up a new generation of consultants and a still newer one of those who will become consultants. These know little of the general practitioner and are unaware of his difficulties. Neither are they aware how easily these difficulties may be increased." My own hope and belief is that already we are seeing a greater understanding than when Hadfield wrote, and that progress towards a better co-ordination of hospital, public health, and general practice will be fostered.

Eighth.—"Finally, when they are beyond help, I still want to offer what solace I may." As Geoffrey Barber says: "In chronic cases it is often said that nothing can be done. General practice consists in doing something to make life as bearable as possible for the patient, and to make him live as comfortably as he can with his disability." "When death comes to a household it is the way in which it is handled by the doctor which can make all the difference between black, unrelieved, and hopeless tragedy, and a sad, but natural event which draws the rest of the family closer together."

These, then, are some of the things I value most in my life as a general practitioner. There are so many sides to general practice. Each has its attraction to someone among those individualists whom we call general practitioners.

Section of Epidemiology and Preventive Medicine

President—Professor A. BRADFORD HILL, C.B.E., D.Sc., Ph.D., F.R.S.

[*November* 19, 1954]

DISCUSSION ON THE ABO BLOOD GROUPS AND DISEASE

(*continued* from February *Proceedings*, p. 139)

Dr. R. B. McConnell gave preliminary data concerning the blood groups of 815 diabetics from the diabetic clinic, David Lewis Northern Hospital, Liverpool.

For analysis the patients were divided into the two main clinical types which are thought to be inherited in different ways, type I by a recessive gene, and type II by a dominant. 30 patients were not classifiable.

In 425 type I cases there were 5% more of group A at the expense of group O than in the control group, but this difference is not significant. In the 131 type I cases in whom the onset had been before the age of 30, there were 12% more of group A than in the controls, and this difference is statistically significant. ($\chi^2 = 8{\cdot}21$). This difference is particularly marked in the males.

In the 360 type II diabetics the blood group distribution is completely normal. The type II diabetics are mainly middle-aged obese women who do not often develop duodenal ulcer even when they are not diabetic. In the younger diabetics the lack of group O may provide the basis for the low incidence of duodenal ulcer.

Dr. C. A. Clarke gave preliminary data concerning the ABO blood group distribution of 1,488 peptic ulcers from three Liverpool hospitals.

In the duodenal ulcers (1,028 cases) 59·6% were group O, and 27·9% group A. In the gastric ulcers (460 cases) 49% were group O, and 40·2% group A.

The control figures taken from 1,000 blood donors from the Liverpool Regional Board Transfusion Service gave 48·10% group O, and 40·60% group A.

These findings, which are in general agreement with Professor Aird and his colleagues (1954, *Brit. med. J.*, ii, 315), suggest that the association between group O and peptic ulcer is much more marked in duodenal than in gastric ulcer.

[*December* 13, 1954]

Environmental Factors in Anæmia and Infection in Pakistan

By G. T. STEWART, B.Sc., M.D., D.T.M. & H.[1]

Visiting Professor of Pathology, World Health Organization
From Dow Medical College, Karachi.

EPIDEMIOLOGY is an old science. Unlike some other old sciences, however, it has always had one great consistency, the concept of environmental causation of disease. In this paper I shall present a summary of my studies on anæmia and infection, two types of illness which are common throughout Asia. My purpose is to see how far the occurrence of such illness can be related to the known dominant environmental factors and to reveal, possibly by default, how much remains unknown and unexplored.

These studies were carried out in Karachi in Pakistan, as part of a WHO teaching assignment, and everything I say represents the work of a team[2] which it was my privilege to lead.

Our methods were simple. We estimated the hæmoglobin levels, and made certain other tests in a group of over 1,000 women. We examined fæces microscopically from another group of over 1,000 men and women. Hospital in-patients, and people who were manifestly ill, were excluded from each group. All the individuals examined were interviewed to obtain factual data about housing, size of family, occupation, wages and so forth. To some extent, our groups were selected, in that we tried to include reasonable minimum numbers

[1] Now at Queen Mary's Hospital for Children, Carshalton, Surrey.

[2] Acknowledgment is made to the following members, who participated in these studies: Professor T. Husain, Dr. S. S. Reza, Dr. A. S. Khan, Dr. S. H. Bokhari, Dr. A. N. Moten, Dr. M. A. Alvi, Dr. S. Bashir Khan, Miss Ruqiya; and to Lt.-Col. S. M. K. Mallick, M.D., F.R.C.P., Principal of Dow Medical College, for his interest and support.

of each age group, income group, &c., so that our results should be as far as possible a fair cross-section of the population.

Anæmia Survey

As might be expected, there was no doubt at all that the hæmoglobin levels in our cross-section of the women of Karachi were very definitely related to their social status. Fig. 1

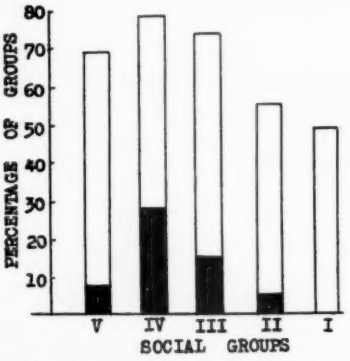


Fig. 1.—Anæmia survey in Karachi. Female subjects of child-bearing age. Relationship between social group and Hb level.

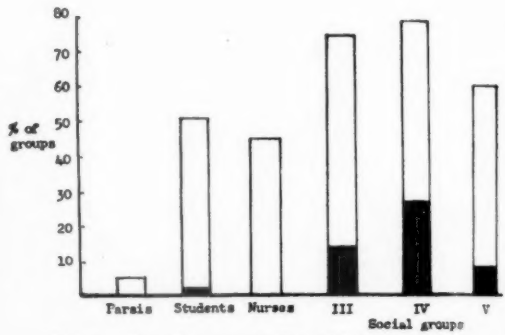


Fig. 2.—Anæmia survey in Karachi. Hæmoglobin levels in different groups of women.

% of groups with Hb less than 80%
% of groups with Hb less than 60%

shows the proportion of women who were anæmic in each of five social groups, ranging from the wives or daughters of wealthy merchants and potentates (group I) at one extreme, to the refugee and beggar class at the other (group V). In the communities amidst which we worked, these various social groups were virtually self-defined, and there was very little overlap between them. Anæmia has been depicted in two grades, the milder type with hæmoglobin values between 60–80% (100%=14·8 grams) and the more severe forms with hæmoglobin values of less than 60%. It must be remembered that all these women were walking and attending to their usual tasks, or, shall we say, carrying their burdens. Yet we find that, in groups III, IV and V, more often than not they were anæmic, sometimes seriously so. In the more fortunately placed groups (I and II), the incidence of anæmia, though hardly negligible, was significantly less.

There was one interesting anomaly which kept reappearing. As we pass from social groups I to IV, the incidence of anæmia increases sharply. But in group V—composed of the wives and daughters of the unemployed, the refugees and the beggars—there was less anæmia than in group IV.

I think there may be a simple explanation of this, but meanwhile let us glance at the results from other environmental angles.

Social status is partly, but seldom entirely, influenced by income. When we analyse our results crudely in terms of income groups we find therefore more anæmia where there is less money. If, however, we refine this analysis (Fig. 2) to the extent of separating out a number of women into communities, irrespective of income, we find that money did not of itself confer—though it may be allied with—what the nutritionists would call Fe value. Our students (Fig. 2) were not necessarily wealthy, and our nurses were not well paid, but they were better placed than their sisters in social groups III–V, even if they did not quite measure up to the irreproachable hæmatological state of the exclusive Parsi community.

If we make allowance for age (Table I) we find that anæmia was most prevalent during the critical period between 15 and 30 years, and showed a significant decline in incidence thereafter. In the physiologically active period, then—and in Asia, women may marry and bear several children before the age of 18—anæmia, often severe, is present in a sizable majority of those women. This prevalence diminishes as we climb the social scale and, incidentally, I might mention that the anomaly of group V, already mentioned, emerges afresh in this closer analysis: it seems that in Karachi, you are wealthier in hæmoglobin at least, if you are the wife of a beggar in group V than if you are the wife of a craftsman in regular employment in groups III and IV. According to local rumour, you may be wealthier in other ways as well.

TABLE I.—ANÆMIA SURVEY IN KARACHI

Mean Hæmoglobin % Levels of Women According to Age and Social Group

	Weighted Means Social group			
Age groups	V and IV	III	II and I	Mean
15–20 years	67%	68%	72%	69%
21–25 ,,	65%	67%	76%	69%
26–30 ,,	65%	66%	76%	69%
31–51 ,,	71%	73%	73%	72%
Over 51	76%	76%	84%	79%
No. of cases	417	296	355	
Means	69%	70%	76%	

I cannot spend time in demonstrating all the factors which we investigated in this survey. But, briefly, pregnancy was found to increase the vulnerability to anæmia at all ages though not necessarily in all communities: some women are only properly cared for when they become pregnant. Among other factors which may be mentioned are Purdah-observance, which was associated with a higher anæmia rate this time in the more privileged, and not in the lowly, social classes. Migration, though significant historically, did not seem to affect Hb values but, oddly enough, the degree of literacy did: at least, literate women in all the social groups were less anæmic than the illiterate. The number of children borne did not seem to matter, but parous women on the whole had lower Hb levels than the nulliparous.

Now it is often said that there is something mysterious and macrocytic about anæmia in the Orient. Our results did not bear this out. Indeed, most of our anæmia was of simple nutritional type and, in the residue, chronic infections such as malaria almost certainly played a large part. True macrocytic anæmia was quite rare, accounting for less than 3% of severe anæmias, and, of course, none of it was Addisonian.

INFECTION

So much for anæmia. Our second survey was designed to estimate the incidence and environmental factors associated with another group of prevalent diseases, intestinal parasitic infections.

The crude carrier rate for various infections is shown in Table II. These estimates were made from single samples of fæces, each sample being subjected to two wet-film examinations and, if these were negative, to concentration by the flotation method. This means that, high as they are, the observed figures must fall short of the actual carrier-rate of each organism. If for example, we take infection with *E. histolytica*, the observed figure was 18·4%. To this can be added, in all probability, the majority of those showing, on one examination. indefinite cysts or exudate, so that the total becomes about 30%. If we had examined more specimens, or if we impose the mathematical correction suggested by Dobell (1916) and others (Stewart *et al.*, 1948), this figure would increase to about 40%. A proportionate increase can be assumed for the other infections listed, so it is obvious that we were dealing with a fair volume of infection.

TABLE II.—CARRIER-RATE OF INTESTINAL PARASITIC INFECTIONS IN MISCELLANEOUS HOSPITAL PATIENTS AND STAFF EXCLUDING CASES OF ACUTE BACILLARY DYSENTERY

Organism	Number of cases	% of total
Entamœba histolytica ..	248	18·4
Indef. cyst and/or exudate	177	13·1
Giardia lamblia	109	8·1
Ascaris	47	3·5
Trichuris	25	1·9
Ankylostoma	22	1·6
Tænia nana	36	2·7
Tænia saginata	6	0·4
Others	293	21·7
Total cases	1,348	

To examine the influence of environmental factors, I have grouped together the total observed figures for all these infections, with a correction to allow for multiple infections. This gives an "infected" and a "non-infected" group, which is useful for the purpose of this paper, though it does not reveal differences which might exist between the various types of infection.

An analysis of the income-groups of the subjects (Table III) shows that infection was

TABLE III.—INCIDENCE OF PARASITIC INTESTINAL INFECTIONS ACCORDING TO INCOME-GROUPS OF SUBJECTS

Rs/month	Less than 40	41–80	81–120	121–200	201–440	Over 440	Total cases
Infected ..	44	279	138	74	19	6	560
	(62·9%)	(59·6%)	(53%)	(63·8%)	(55·9%)	(37·5%)	
Not infected	26	189	122	42	15	10	404
	(37·1%)	(40·4%)	(47%)	(36·2%)	(44·1%)	(62·5%)	
Total cases	70	468	260	116	34	16	964

widespread at all levels, and that there was no significant difference in the incidence of infection between the lower and middle income groups at least. Freedom from want does not apparently confer freedom from amœbiasis.

TABLE IV.—INCIDENCE OF PARASITIC INTESTINAL INFECTIONS ACCORDING TO HOUSING CONDITIONS OF SUBJECTS

	Refugee huts	Urban slums	Middle-class and residential	Total cases
Infected ..	121 (56%)	195 (58%)	78 (59%)	394
Not infected	97 (44%)	139 (42%)	55 (41%)	291
Total cases	218	334	133	685

In this part of our survey we were for various reasons unable to obtain the same amount of social and environmental data about our cases as in the anæmia surgery. In the remaining figures, therefore, the data have had to be simplified, and the numbers are smaller but still, I think, sufficient for comparisons to be made. For instance, we imagined that infection might be related to housing conditions so, instead of dividing our cases into their various social grades, we divided them according to the types of dwellings they inhabited (Table IV). It appeared that the incidence of infection was remarkably uniform, that you were as likely to find intestinal parasites in the residential suburbs as in the slums.

TABLE V.—INCIDENCE OF PARASITIC INTESTINAL INFECTIONS ACCORDING TO NUMBER OF INDIVIDUALS PER ROOM

No. per room	6 or more	3–5	2	1 or less	Totals
Infected subjects:					
Number:	23	107	36	6	172
% of infected group	13%	62%	21%	4%	
% of housing group	59%	59%	61%	55%	
Not infected:					
Number:	16	74	23	5	118
% of group	14%	63%	19%	4%	
% of housing group	41%	41%	39%	45%	
Totals	39	181	59	11	290

To investigate this aspect in closer detail and, necessarily, with much smaller numbers, we then classified our cases in terms of crowding in their homes (Table V). Again we met with a striking and quite unexpected uniformity in the incidence of infection.

These then are the facts of our study and, as such, I trust they are unambiguous. If by anæmia we mean a hæmoglobin value of less than 80% (11·8 grams %), then anæmia was very prevalent indeed in a cross-section of the female population of Karachi in that it affected nearly half of the women in the wealthy class and 75% of those in the artisan class. I am fairly confident about these figures but I have to confess that I am less confident about the word anæmia. For instance, the hæmoglobin value of 100% (14·8 grams %) is based upon the average value of male subjects in the Western world. With Asiatic males in Karachi, we found that more than half had hæmoglobin levels of less than 100%, the median value being only 92%. Among European females, we found that nearly three-quarters had values just below 80%. All of these estimations were made upon apparently healthy, active subjects, and I do not pretend to know what is the explanation; but it is possible that climate, hydration, locality and other factors peculiar to the latitude—and perhaps the longitude—were somehow involved.

Be that as it may, we can drop our Western ideas about 100% hæmoglobin quite considerably, and still have to admit, from the figures submitted, that anæmia in Pakistan is a real problem, for there would seem to be millions walking, working and bearing children with hæmoglobin values of less than 50% (7·4 grams %). Since most of this anæmia is nutritional in type, it is not surprising to find that its incidence runs parallel to the major social factors which I have mentioned—poverty, child-bearing, the low status of women in certain communities. Even so, the extent to which the already high incidence of anæmia increases in the physiologically active age period (15–30 years) and in pregnancy, especially in its third trimester, seems to me quite startling and not confined in its effect to this generation only. Paradoxically, the incidence of anæmia lessens significantly in the lowest social strata, among the wives of beggars and unemployed refugees, indicating possibly that some subtle urban stresses, absent in these people, may contribute to the higher incidence in the artisan classes above. This, however, was the only important exception which we encountered. In other respects, anæmia appeared to be a fairly exact mirror of environmental conditions.

In complete contrast, we found that parasitic intestinal infection, also a widespread disease, was unrelated in incidence to differences in income, community or type of home. It seems therefore that infection breaks through the social structure of the country, whereas anæmia is caused by it.

Now it is tempting to think that a little sensible social medicine could explain these differences and rectify these wrongs. And, indeed, there are obviously a number of simple

solutions, which, aimed though they are from a distance of 7,000 miles cannot be altogether wide of the mark. For example, it would not be difficult to define, here and now, the groups most vulnerable to anæmia. In fact, one might say that the answer to nutritional anæmia lies largely in the pockets of those unaffected by it. Or, with regard to infection, one could justifiably suggest that when the volume of infection reaches a certain level, environmental barriers to its spread begin to break down; that a massive influx of refugees (there are over half a million in Karachi) may so strain housing and sanitary resources that isolated foci of infection become confluent, and common to all; that the rich are, after all, served at table by the poor, in Asia if not in England. All these are, I repeat, simple answers which cannot be seriously wrong. But it would be an injustice to the complexity of life in the countries concerned to suggest that they are the proper answers. At the risk of sounding quite unscientific, I am going to say that you cannot give health to Asia by a touch of Western epidemiology here and there. I do not think that we can cure the malnutrition in Indo-Pakistan by powdered milk from the U.S.A. or by iron supplements from England.

I began this address by implying that there might be contradictions to the important rule that preventable environmental factors induce community diseases. The problems and paradoxes which I have mentioned are not such as to dislodge such a rule, but they do perhaps qualify its applicability here and there. Translated from figures and charts into human and economic terms, they are the kind of challenge that, in the small world of to-day, one cannot readily ignore.

REFERENCES

DOBELL, C. (1916) *Spec. Rep. Ser. med. Res. Comm.*, No. 4.
STEWART, G. T., O'MEARA, P. J., and KERSHAW, W. E. (1948) *J. R. N. med. Serv.*, **34**, 2.

Dr. S. S. Reza: The result of the survey leaves little doubt that the severe degree of anæmia is connected with the economic state of the masses.

The widespread mild anæmia according to the accepted hæmoglobin standard may be peculiar to that part of the world for socio-economic reasons or the accepted hæmoglobin standard may be too high for the population, since they manage to live a normal life for all practical purposes with about 11·8 grams % hæmoglobin.

Further investigation is required to assess the normal hæmoglobin value for that part of the world.

The Measurement of Malaria Transmission

By G. MACDONALD, C.M.G., M.D.

Director, Ross Institute of Tropical Hygiene, Professor of Tropical Hygiene, University of London

Two full malaria surveys have been made by my colleagues Davidson and Draper (1953) and Davidson (1955) on principles derived from a theoretical analysis of the mathematical nature of transmission prepared by myself (Macdonald, 1950, 1952 *a*, *b*). The work was carried out in two parts of East Africa, in Tanganyika and Uganda, where malaria transmission is perennial and holo-endemic, or of an extreme and continuous intensity which has been much studied in near-by localities (Wilson, 1936, 1939; Garnham, 1929, 1949; Wilson *et al.*, 1950, &c.). The predominant parasite is *Plasmodium falciparum*, the incidence of infection by ages is shown in Table I, and the type of endemicity is particularly characterized by its stimulation of an immunity manifested by a marked decrease in parasitic density from the age of about 2 years onwards, and a slower progressive reduction in the parasite rate which can be seen in Table I.

TABLE I.—SPLEEN AND PARASITE RATES, TANGANYIKA AND UGANDA

	Tanganyika			*Uganda*		
Age group	No. exam'd.	Spleen rate %	Crude parasite rate %	No. exam'd.	Spleen rate %	Crude parasite rate %
2 weeks to 2 months	109	18	21	31	34	61
3 to 5 months ..	57	69	75	72	75	81
6 to 11 months ..	74	87	88	98	89	92
1 to 23 months ..	62	89	87	150	94	99
2 to 4 years ..	89	89	96	266	88	98
5 to 10 years ..	192	73	85	211	68	95
11 to 14 years ..	78	53	74	36	31	81
15 years and over ..	83	26	42	57	20	33

Malaria is transmitted by two mosquitoes: *Anopheles gambiæ* and *A. funestus*, the densities, biting habits and infection rates amongst which were studied by traditional means with results which are set out in Table II. Their implications may be illustrated by reference to

TABLE II.—DATA ON ANOPHELINE PREVALENCE AND INFECTION

	Tanganyika (Mngeza)		Uganda (Lira)	
	A. gambiæ	*A. funestus*	*A. gambiæ*	*A. funestus*
Mosquito density (per person) ..	4·25	50	3·2	3·1
Man-biting frequency (per day) ..	0·5	0·5	0·5	0·33–0·5
Sporozoite rate (proportion) ..	0·047	0·034	0·146	0·062
"Infective" bites per person per day ..	0·1	0·85	0·23	0·06–0·1

NOTE.—Mosquito density in the Mpakane area in Tanganyika was less than in Mngeza, about half. Mngeza data are given for illustration.

the Tanganyika findings which show that the average individual is bitten every day by about 25 mosquitoes which have an infection rate of about 4%. On the average therefore each individual is bitten by about one infected mosquito daily. In the Uganda survey the figure is rather less, about one infective bite every three days, but both of these series of records conjure up a picture of extremely frequent transmission, on an almost fantastic scale which is, however, generally accepted as the typical picture of transmission in these areas.

The most novel technique used was the measurement of the mortality of the mosquito vectors in nature; to achieve this was itself a major problem and the means used are described elsewhere (Davidson, 1953, 1954, 1955). It is sufficient here to say that we are confident it has been measured within reasonably narrow limits of error. The expression used is the probability of survival through one day (p) which is clearly the complement of the probability of dying. The values recorded for the two species in the two surveys are shown in Table III, together with some implications from the rates, which are, incidentally, materially independent of age. The parasite of malaria must undergo an incubation in the mosquito before it becomes infective to man, the necessary period, indicated as n days, being thirteen days in the environment of the Tanganyika survey and fourteen in the Uganda example. The third column in Table III shows the proportion of mosquitoes which might be expected to

TABLE III.—THE PROBABILITIES OF ANOPHELINE SURVIVAL IN TWO SURVEYS

Area and species	Probability of survival for 1 day p	Probability of survival for n days p^n	Expectation of life $\frac{1}{-\log_e p}$	Combined probabilities $\frac{p^n}{-\log_e p}$
Tanganyika:				
A. gambiæ ..	0·93	0·39	13·8	5·4
A. funestus ..	0·92	0·34	12·0	4·1
Uganda:				
A. gambiæ ..	0·97	0·65	32·8	21·4
A. funestus ..	0·93	0·36	13·8	5·0

NOTE.—The value given to n is 13 in the Tanganyika series, and 14 in the Uganda series.

survive through this period after feeding on a case, the fourth the subsequent expectation of life of such as do, whilst the last gives the combination of the two, a probability of survival for n days and subsequent expectation of life. These last are considerable and indicate the expectation of survival in the infective state of a mosquito which has taken one infective feed. Under the conditions of the greater part of these surveys the mosquitoes fed on man typically once in every two days, and the number of bites which a mosquito which had once fed on a case might later be expected to inflict on man whilst harbouring mature and possibly infective parasites is half the figure given in the last column.

If the counts of anophelines biting shown in Table II are considered in relation to these figures another picture of intense and extremely frequent transmission is built up. Again illustrating from the Tanganyika figures, a case of malaria might typically be bitten every day by about 25 *A. funestus* with a mean expectation of 4 days of life after survival long enough for maturation of the parasite. Since this species is here biting man once in every two days a case of malaria might be said to make effective contact *via* vector mosquitoes with about 50 other people on every day of its continuation. A picture of extreme potential multiplication of cases is thereby built up and is only exaggerated by the realization that the measurements we have of the duration of the disease, which come from temperate countries,

indicate a duration of many weeks—perhaps about eighty days. It is known that immunity restricts this duration in Africa but any degree of restriction previously considered would leave the picture of prolific multiplication almost untouched.

However, the examination can be pushed deeper, when it shows a picture in sharp contrast to the accepted one which is illustrated above. Perhaps the most fertile single concept of analysis is the reproduction rate of disease, just as it is the most fertile in demography, and with very closely comparable meanings and implications. It may be defined as the number of infections distributed in a community by a case with attributes which are the mean of all those actually occurring. It may be expressed as a gross or a net rate as in the demographic expression but its most useful expression is slightly different. It has a ready mathematical expression (1), and two limits, one when there is no other previously infected person or mosquito in the community (2) which is termed the basic reproduction rate[1] and one of 1·0 when equilibrium is established. [(1), (2), etc. These refer to notes in the Appendix, p. 300.] The basic rate is the most generally useful, subsequent reference is exclusively to it, and in distinction to the demographic rates it is the critical one as its value determines the continued existence of the disease. The critical level is 1·0, rates below which determine the progressive elimination of the disease.

The actual values of the basic rate can be studied as a whole, because it enters into several fairly readily measured rates (3) from which it can be derived, and it can be dissected into its component parts. The reverse process of synthesis from its components is possible but more subject to error, oddly enough largely due to the potential error in the most direct measurement made, mosquito density.

The most convenient and accurate method of measurement as a whole is by the use of the expression:

$$z_o = \frac{p^n}{p^n - s}$$

where z_o is the basic reproduction rate.
p is the probability of survival through one day.
n is the incubation period to infectivity in the mosquito.
s is the proportion of mosquitoes with sporozoites in their glands.

It is believed that p^n and s have been measured with considerable accuracy. Where two mosquito species are concerned a mean value should be derived, and they are, in fact, very similar. Taking data for *A. gambiæ* from Davidson and Draper's Tanganyika survey, p^n is 0·39 with a standard error of 0·04 and s is 0·047 with a standard error of 0·008. From these the value of the basic reproduction rate can be calculated as 1·15, with a standard error of 0·09. No emphasis is here placed on any precision of value, but merely on its order, only slightly above its critical level of 1·0. The comparable figure for Davidson's Uganda survey is 1·25, of the same order, and with the same degree of accuracy. The similarity is the more remarkable from the fact that when dissected into their component parts, the individual factors have quite different values, as may be seen in Tables II and III, but they manage to combine together to produce the same end-result.

Almost identical data have been collected in the Belgian Congo by Vincke (1946) though they have not before been analysed in this way; the value of the basic reproduction rate deduced from them is 1·1, again almost the same though the components are different. Comparable data which can be used in a similar way though with less accuracy have been collected in many previous surveys, and all those examined from Africa result in the production of similar values, such as 1·2 in Lagos, Nigeria (Barber and Olinger, 1931), 1·05 in Liberia (Barber *et al.*, 1932), 1·15 in Kissy, Sierra Leone (Gordon *et al.*, 1932). The only marked divergence concerning *gambiæ*-carried malaria is a value of 3·6 derivable from data by Davis (1931) during an epidemic following the recent introduction of that species into Brazil. So far as the static and hyperendemic conditions of Africa are concerned it seems that the potentially very high basic reproduction rate is automatically adjusted by some governing mechanism to lie just above its critical value of 1·0, and that this adjustment occurs whatever the value of the primary factors controlling transmission. This picture is very different from the impression given in the first two approaches made. It is to be emphasized that the first two approaches gave impressions which remain as such despite the general acceptance of their implications, because they include assumptions of infectivity which cannot in the end be substantiated and which are examined below.

The infectivity of man may be considered in a number of ways, but perhaps best as the proportion of feeds on the general population which cause infection of the mosquito at any

[1] In a previous paper (Macdonald, 1952*b*) this was defined with reference to infections distributed by a non-immune case, a fixed value of the recovery rate applicable to non-immunes being used. It is more useful with a fully variable value and the previous definition is abandoned.

one feed. It is taken in this way because some infections may occur despite the fact that parasitological examination fails to demonstrate either the infective form, the gametocyte, or asexual forms. This figure can be derived from knowledge of the sporozoite rate and biting habit of the mosquito and its probability of survival (4). This approach indicates that about 2% of feeds result in infection of the mosquito in Tanganyika and between 2 and 4% in Uganda, and this despite the fact that 80 to 100% of children and 30 to 40% of adults in both areas showed malaria parasites in their blood. The figure is derived in this way because the indirect approach is for various reasons looked on as more accurate than the direct one which, however, fully supports its findings. Thus Draper (1953) in original studies on this subject by feeding experiments in a similar area of West Africa concluded that 0·5% of feeds caused infection, and from similar data that the values in Tanganyika and Uganda were 1·6 and 3·6%, very similar to those given by the indirect approach.

Infectivity can also be expressed as a recovery rate from infectivity, in which form it appears in the mathematical expression, and an approximation to it can readily be derived (5) since the inoculation rate is known (*see below*). The recovery rate is about 0·47 in Tanganyika and 0·5 in Uganda, which means that on the average a single case of malaria will infect as many anophelines as feed on it in two days' time.

This increase in the recovery rate, for the value in non-immunes may be of the order of 0·0125, must substantially reduce the reproduction rate from its potential value, to about one-fortieth, but if this were all, transmission would still remain intense, in the Tanganyika example one case distributing about 100 infections instead of the 1·1 indicated by the reproduction rate, and there must be another mechanism of reduction at work.

It lies in reduced infectivity of the mosquito which may be studied in the following way. Fig. 1 shows a curve of the infant parasite rates from birth onwards in the Uganda series

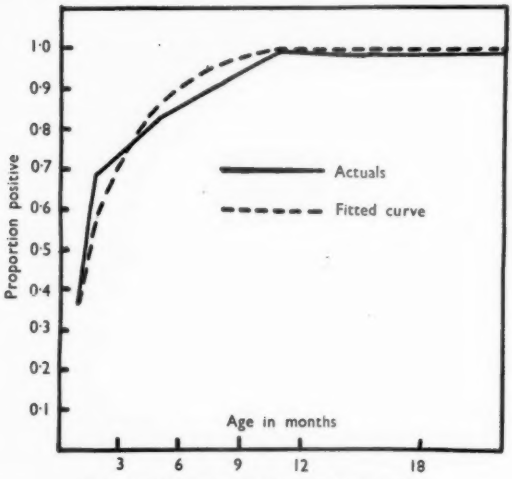


FIG. 1.—Infant parasite rates in Uganda.

and based on 463 examinations together with a fitted curve (6) which corresponds to an inoculation rate of 0·015, or one successfully implanted infection every sixty-seven days. This figure is very different from the corresponding one of one infection every three days, derived by traditional means from mosquito density and infection rates and given for the same area in the opening paragraphs. In the Tanganyika series the discrepancy between the two methods of estimation is even greater, 0·0094 and 0·95.

The fitted curve does not depend on any numerical assumption whether of the recovery rate or other factor. The only assumption in it which could be the subject of controversy is that superinfection can happen. If this were rejected no curve could be acceptedly fitted, and because many such comparisons have been made it seems certain that the original assumption of superinfection must be accepted. In fact no acceptable mechanism can be framed which explains this curve of the infant parasite rate on an inoculation greatly different from that postulated, 0·015, and the same holds for the Tanganyika curve which it resembles. There can be no reasonable doubt that the discrepancy is actual and lies between successfully implanted infections shown by the technique here described, and apparent infections shown

by the first. In Uganda 19 out of 20 apparent infections fail in implantation, and in Tanganyika 99 out of 100.

There are many possible reasons for failure of infectivity, the relative insusceptibility of corpuscles containing fœtal or sickling hæmoglobin, deficiency of para-aminobenzoic acid in the mother's milk, a passive immunity transplacentally transferred, or, of course, low density of infections in the mosquito. It is probable that more than one of these factors play a part, but the variations in the degree of discrepancy found in different parts of Africa, some of which have been displayed previously (Macdonald, 1952*b*), demand some explanation which differs greatly in degree from place to place. It has been amply shown that infectivity is a function of density of infection, even though experimental work has necessarily been confined to mosquito infections 20 to 50 times as dense as those typical of this area, where the oocyst counts are very low. Some considerable weight must be given to this factor in explaining the extremely common failure of infection. It appears very probable that the mechanism lies in reduction of infectivity of the human case, which particularly takes the form of reduction of gametocyte density, with the result that (*a*) the great majority of feeds on infected individuals do not result in infection of the mosquito, as already shown, and (*b*) those which do, result in typically very scanty infections of the mosquito of which only a very small proportion are passed on to man.

The extraordinary uniformity of the basic reproduction rate which has already been commented on shows that these effects are not haphazard but in finely balanced proportion to the weight of infection experienced by the people. Though immunity is demonstrable by the usual parasitological means its principal manifestation lies in a reduction of human infectivity. The greater the weight on the population the more rapidly and effectively is this reduction achieved and it only comes to an end when actual successful transmission is almost damped out of existence. In result there is a balancing mechanism which keeps transmission just over what would be, for that particular community, its critical or extinction level. The actual residual transmission is admittedly very frequent by the standards of the non-immune, but by the standards of the local inhabitant it remains low. This mechanism, can, of course, be upset in two ways: interruption of transmission allows the growth of a non-immune group of infants which may soon be quite big enough to magnify the reservoir of truly non-immunes in this sense, and the same effect may be caused by the influx of large numbers of non-immunes which is well known to disturb the balance.

Apart from the satisfaction in understanding happenings there are a number of practical implications from these conclusions. Control which is only partially effective can only reduce the stimulus to immunity and by adjustment the reproduction rate will remain unaltered. Transmission may thus become numerically less frequent but will remain, so far as that community is concerned, at the same level. The only escape is by control which will keep the reproduction rate under control without the incidental help of immunity and fortunately our technological knowledge is equal to this. In such control the all or nothing law operates, as much previous experience has shown; but all is now possible.

This is infinitely the most potent curb on transmission, but there are two others which deserve brief mention, though they do not curb the reproduction rate but rather its influence on the proportion of infected people in the population, which I term the endemic level. One is well acknowledged, the absorption of susceptible individuals, and needs little statement except that it is relatively ineffective in a disease in which superinfection can occur. The other is absorption of the susceptible mosquitoes, a concept which is new to most but clearly an inevitable one in this context, and the influence and form of which are beautifully shown in the mathematical workings. Its major interest lies in the fact that its influence varies greatly under different circumstances, for the infection rate amongst mosquitoes does not show the same relationship to the parasite rate in man in different places. The difference between such places lies either in the longevity or in the man-biting habit of the mosquito, low values of which minimize the chance of superimposed infections in the mosquito and to all intents and purposes put this curb out of action, whereas high values make them common and reinforce this curbing mechanism. Its mathematical expression is simple—the curb operates in direct proportion to the mean number of feeds taken on man by a mosquito during its lifetime—or to translate it literally the sensitivity of the endemic level to changes in the basic reproduction rate is inversely proportional to this mean number (7). One can therefore define an index of sensitivity which is the converse of this value—when the index is high the curb does not operate effectively and small changes in the basic reproduction rate have a great effect on the endemic level, and vice versa. In the two East African surveys figures have been derived from two species, 0·15 and 0·16 for *A. gambiæ* and *A. funestus* respectively in Tanganyika and 0·06 and 0·18 in Uganda. All of these values are extremely low, and perhaps they represent the lower limit of what is found anywhere in the world. They indicate that a change in the basic reproduction rate will produce a proportionately smaller change in the endemic level and so will not greatly disturb the equilibrium unless it is itself very great.

This insensitivity is the predominant characteristic of malaria in these areas. It may be contrasted with the highly sensitive and frequently epidemic malaria in other places such as the plains of India, in a part of which a comparable index of sensitivity of approximately 20, roughly 200 times as high, can be derived from similar data collected by Russell and Rao (1942).

The general numerical pattern of transmission in these areas is that external conditions would favour transmission on a fantastically high scale but for the working of immunity; the development of immunity is demonstrable in rough outline by parasitological studies but the present studies show that it is very finely adjusted and, in fact, permits what is to the population concerned only a minimal amount of transmission. The mechanism is by rapid and dramatic curtailment of the gametocyte output after short exposure to the prevailing intensity of transmission and in proportion to it. Variations in the reproduction rate are, of course, inevitable with rapid changes in mosquito output and other factors, but under local conditions (and not as a general matter) such changes produce little effect on the endemic level and in consequence marked fluctuations in incidence are unknown. Malaria carried by anophelines with other characteristics does, however, fluctuate very violently in response to even minor changes in the basic reproduction rate, and in consequence malaria varies very greatly in its stability from place to place.

REFERENCES

BARBER, M. A., and OLINGER, M. T. (1931) *Ann. trop. Med. Parasit.*, **25**, 361.
——, RICE, J. B., and BROWN, J. Y. (1932) *Amer. J. Hyg.*, **15**, 601.
DAVIDSON, G. (1953) *Nature, Lond.*, **172**, 503.
—— (1954) *Nature, Lond.*, **174**, 792.
—— (1955) *Trans. R. Soc. trop. med. Hyg.*, **49**. In press.
——, and DRAPER, C. C. (1953) *Trans. R. Soc. trop. Med. Hyg.*, **47**, 522.
DAVIS, N. C. (1931) *Riv. Malariol.*, **10**, 43.
DRAPER, C. C. (1953) *Trans. R. Soc. trop. Med. Hyg.*, **47**, 160.
——, and DAVIDSON, G. (1953) *Nature, Lond.*, **172**, 503.
GARNHAM, P. C. C. (1929) *J. trop. Med. Hyg.*, **32**, 207, 221.
—— (1949) *Ann. trop. Med. Parasit.*, **43**, 47.
GORDON, R. M., HICKS, E. P., DAVEY, T. H., and WATSON, M. (1932) *Ann. trop. Med. Parasit.*, **26**, 273.
MACDONALD, G. (1950) *Trop. Dis. Bull.*, **47**, 907, 915.
—— (1952*a*) *Trop. Dis. Bull.*, **49**, 569.
—— (1952*b*) *Trop. Dis. Bull.*, **49**, 813.
—— (1953) *Trop. Dis. Bull.*, **50**, 871.
RUSSELL, P. F., and RAO, T. R. (1942) *Amer. J. trop. Med.*, **22**, 517, 535.
VINCKE, I. H. (1946) *Ann. Soc. belge Med. trop.*, **26**, 384.
WILSON, D. B. (1936) Report on the Malaria Unit, Tanga. Dar-es-Salaam, Government Printer.
—— (1939) *Trans. R. Soc. trop. Med. Hyg.*, **32**, 435
——, GARNHAM, P. C. C., and SWELLENGREBEL, N. H. (1950) *Trop. Dis. Bull.*, **47**, 677.

APPENDIX

NOTES ON THE MATHEMATICAL STATEMENTS IN THE TEXT

Symbols are used with the following meanings:

- m The anopheline density in relation to man.
- a The average number of men bitten by one mosquito in a day.
- b The proportion of those anophelines with sporozoites in their glands which are actually infective.
- p The probability of an anopheline surviving through one day.
- n The time taken for completion of the extrinsic cycle.
- s The proportion of mosquitoes with sporozoites in their salivary glands.
- h The proportion of population receiving infective inocula in one day.
- x The proportion of the people affected (here in the sense of being actually infective to mosquitoes except in (6) below where it is the proportion with parasites in the blood)
- L The limiting value of the function given as a subscript, as L_x — the limiting value of x.
- r The proportion of affected people who revert to the unaffected state in one day, here used in the sense of recovery from infectivity.
- z The reproduction rate, and z_o its limit as x approaches zero, or the basic reproduction rate
- t Time in days.
- e The base of natural logarithms, 2·71828.

(1) *The Reproduction Rate*

In the course of its time of infectivity ($1/r$) a case will be bitten each day by ma mosquitoes of

which the proportion not yet infected will be $(1 - ax/ax - \log_e p)$. The proportion of these surviving for n days is p^n, and their subsequent expectation of life is $\frac{1}{-\log_e p}$. During this time they will bite a times each day, and the proportion b of these bites will be infective, whence

$$z = \left(1 - \frac{ax}{ax - \log_e p}\right)\frac{ma^2bp^n}{-r\log_e p} \qquad \text{.....(1)}$$

(2) The limit of the above rate as x approaches zero is

$$\frac{ma^2bp^n}{-r\log_e p} \qquad \text{.....(2)}$$

which is termed the basic reproduction rate, designated z_o.

(3) It has already been shown (Macdonald, 1952*a*, *b*) that

$$s = \frac{p^n ax}{ax - \log_e p} \qquad \text{.....(3)}$$

and that, when less than 1·0

$$L_x = \frac{mabp^n}{r} + \frac{\log_e p}{a} \qquad \text{.....(4)}$$

By the substitution of the value of (2) above in (4) it can be shown that

$$L_x = \frac{-\log_e p}{a}\left(z_o - 1\right) \qquad \text{.....(5)}$$

If this limiting value of x is substituted in (3) above it can equally be shown that the limiting value of s is given by

$$L_s = \frac{p^n}{z_o}\left(z_o - 1\right) \qquad \text{.....(6)}$$

whence

$$z_o = \frac{p^n}{p^n - L_s} \qquad \text{.....(7)}$$

provided $x < 1{\cdot}0$, in which case $z_o < \frac{a - \log_e p}{-\log_e p}$

(4) From (3) above

$$x = \frac{-s\log_e p}{a(s - p^n)} \qquad \text{.....(8)}$$

(5) It has been shown (Macdonald, 1950) that

$$L_x = \frac{h}{r} \qquad \text{.....(9)}$$

whence

$$r = \frac{h}{L_x} \qquad \text{.....(10)}$$

The mean value of x is taken as a rough index of L_x, and hence the statement in the text that an approximation to r can be derived in this way.

(6) The curve is fitted on the expression

$$x = 1 - (1 - x_o)e^{-ht} \qquad \text{.....(11)}$$

which was established by Macdonald (1950).

(7) The effective expression is given in (5) above,

$$L_x = \frac{-\log_e p}{a}\left(z_o - 1\right)$$

whence

$$\frac{d(L_x)}{dz_o} = \frac{-\log_e p}{a} \qquad \text{.....(12)}$$

which last is therefore a measure of the variation of L_x in association with that of z_o, or an index of sensitivity. It may be noted that $a / -\log_e p$ indicates the average number of feeds taken on man in the course of a mosquito's life, and hence the statement that sensitivity is inversely dependent on this figure.

Mr. P. G. Shute: If at the present time we possessed the perfect imagocide and larvicide which were so cheap that they could be used even wastefully by unskilled labour in poverty-stricken malarious parts of the world, the biological side of malaria control would not be essential. But this ideal has not yet materialized and it seems to me that biological research is as important as ever it was, especially the study of gametocytes in its widest sense. I think this statement is justified in view of the fact that we now have two drugs (proguanil and pyrimethamine) which have the property of arresting sporogony in the mosquito. The combination of mosquito control with the administration of drugs which sterilize the gametocytes could form a powerful combination in malaria control schemes.

When we began our malaria work for therapy purposes in 1923, we used Darling's findings for deciding whether a patient showed a sufficient number of gametocytes to justify feeding a batch of mosquitoes. His figures were 12 males and 12 females per c.mm. of blood. His work referred to *falciparum* gametocytes whereas we were at that time working with *vivax* malaria. With these counts we often had twenty or more oocysts per gut. We found that the greatest density of gametocytes in true primary malaria in non-immune untreated patients occurred on or about the eighth day of fever. For years we worked on this basis but a few months ago it was decided to begin an investigation to find out the earliest day that a primary case of *vivax* malaria could infect mosquitoes. To our great surprise we are finding that infection sometimes occurs on the third day of fever and parasitæmia. What is so interesting about this is that we are unable in most cases to find gametocytes in two or three thick and thin films. We are now investigating the possibility of greater gametocyte density immediately under the skin as suggested by Louis van den Berghe and Marcel Chardome (1951, *Amer. J. trop. Med.*, **31,** 411).

In view of the above and other findings, not yet published, it would seem that reports of malaria surveys in which the percentage of the population which could infect mosquitoes is calculated from the result of blood examinations may be misleading. I would suggest that a more accurate measurement would be to estimate the infectivity of susceptible anophelines by sample feeding. The technique is quite simple, especially if the mosquitoes are not dissected until about the sixth day after feeding when the oocysts are easily seen with the 1/6th dry lens.

I believe that work on these lines would produce valuable information and I agree with Professor MacDonald when he states that the best way of determining the infectivity of man is by finding the proportion of feeds on the general population which result in infection of the mosquito. Where gametocytes are numerous in a thin film, generally speaking a susceptible carrier will become heavily infected. But it is the scanty gametocyte carriers which infect perhaps only 1 or 2% of the mosquitoes with only one or two oocysts which may be of greater importance in holo-endemic areas because they greatly exceed the few who show numerous gametocytes.

It is now generally accepted that in all forms of human malaria gametocyte density is higher in primary attacks in non-immune subjects than it is in relapses or in chronic carriers. But this is not all. In non-immunes where malaria is not endemic, gametocyte density (of any species of parasite) is much higher than it is even among infants in holo- or hyper-endemic areas. Is this, I wonder, evidence of some degree of racial tolerance among infants in highly malarious areas? If this is so, the influx of non-immunes even in small numbers would undoubtedly disturb the balance, as suggested by Professor MacDonald.

The importance of the longevity of an infected mosquito is relative to its degree of infection (quantum of sporozoites). On numerous occasions I have counted over 1,000 oocysts on a single gut in both *vivax* and *falciparum* infections. If, then, each oocyst produces approximately 10,000 sporozoites this means that the mosquito manufactures about ten million sporozoites and the whole of the body becomes infested; maxillary palps, legs and wings as well as the salivary glands. Such heavily infected mosquitoes never become completely negative even if they live and feed frequently for several months. We have successfully infected 15 patients in succession by the bites of one mosquito which fed on alternate days over a period of one month.

On the other hand, with *P. malariæ* in which fewer gametocytes are produced than in any of the other forms, we have never seen oocysts in double figures. Moreover, in those infected, the salivary glands became negative after one, or at most two, feeds. It seems likely that this may also be a frequent occurrence in the case of holo-endemic *falciparum* malaria.

Section of Pædiatrics

President—G. H. MACNAB, M.B., F.R.C.S.

[*October* 27, 1954]

Intestinal Obstruction in the Newborn

PRESIDENT'S ADDRESS

By G. H. MACNAB, M.B., F.R.C.S.

IN order to review the subject of intestinal obstruction occurring in the newborn, I shall call on the experience of my colleagues at the Hospital for Sick Children, Great Ormond Street, for the condition is uncommon and does not permit of the collection of a large personal series of cases (Fig.1).

The first important observation that arises from our experience is that, in the intrinsic type of case, acute intestinal obstruction does not occur in the neonate. We are looking at a chronic intestinal obstruction which has been forming over a period of months, and the sudden ingestion of food proves to be the breaking point. Meconium is the product of secretions from the stomach, intestine, liver and pancreas, dead cells from the lining of the intestine, and traces of amniotic fluid swallowed by the infant containing cornified epithelial cells desquamated from its skin. Meconium begins to form in the third month of life, reaches the level of the ileo-cæcal valve by the fourth month, and is present in the colon by the fifth month. This state of affairs explains the common finding of peritonitis, associated with perforation, in intestinal atresia.

Meconium peritonitis can occur before birth, but we do not yet know the true ætiology. It has been suggested that the final stages of rotation of the intestine are not complete, so that partial volvulus may occur on a pedicle of mesentery; meconium is held up leading to distension of a segment of bowel with resultant anoxia of its wall and perforation. The sterile meconium, by its irritant action, seals the perforation and sets up adhesions which fix the rotating bowel, so that the infant is born and lives with a good functioning intestinal tract. The only evidence of this intra-uterine catastrophe may be calcification in the peritoneal cavity seen on X-ray after birth.

It is interesting to note that the slow formation and passage of meconium through the intestine *in utero* is essential for dilatation of the gut to prepare it for its proper function,

NEONATAL OBSTRUCTIONS (1926-51)

OESOPHAGEAL OCCLUSIONS			52
INTESTINAL OBSTRUCTIONS 222	INTRINSIC 104	ATRESIAS & STENOSES	79
		MECONIUM ILEUS	13
		NEONATAL HIRSCHSPRUNG'S	12
	EXTRINSIC 118	VOLVULUS PERITONEAL BANDS & MESENTERIC MALFORMATIONS	62
		NEONATAL INTUSSUSCEPTION	4
		DIAPHRAGMATIC HERNIA	9
		INGUINAL HERNIA - Strangulated	17
		INTERNAL HERNIA	4
		EXOMPHALOS - with obstruction	4
		MISCELLANEOUS	18
ANO-[illegible]TAL MALFORMATIONS - requiring immediate operation			85
		TOTAL	359

FIG. 1.—359 cases of neonatal intestinal obstruction. Louw's table of analyses.

FIG. 2.—Distended blind end with gangrene present. Atresia of small intestine.

so that a meconium stool is passed in the first twenty-four hours of life. Failure of the passage of meconium is due to an area of atresia so that the bowel below it remains in a contracted state.

Recent observation has shown that the passage of normal meconium will dilate up the distal bowel in a short time following removal of the mechanical obstruction. Knowledge of the time of formation of meconium and the effect of its passage on the bowel has led to new ideas on the treatment of single areas of intestinal atresia, which has lowered the operative mortality at Great Ormond Street from 75% to 30%.

In atresia of the duodenum or small intestine, the blind end is always grossly dilated. Pressure set up by the blocked meconial content causes vascular changes, so anoxia of the bowel wall is present and may lead to gangrene and perforation (Fig. 2). At operation the blind distended end often has a cyanotic tinge but normal peristaltic movement appears to be present and it is considered to be viable. End-to-end anastomosis following local resection of the atretic area did not cause meconium to be passed, and X-ray evidence suggested that intestinal obstruction had not been relieved. The surgeon was then faced with a second operation believing that his narrow anastomosis was blocked by œdema. He would either free coils of intestine tacked on to the anastomosis and thought to be kinking it, or perform a second anastomosis. As no improvement then took place it was thought that paralytic ileus was present due to proximal bowel of poor tone having to work against a contracted distal bowel plugged with sticky stagnant meconium. The next step was to carry out temporary enterostomy proximal to the anastomosis after resection of the atretic area, but this procedure did not lead to success, and so was followed by double enterostomy with aspiration of proximal bowel and injection of meconium into distal bowel. This latter procedure failed as the dilated proximal bowel was so devitalized that it would not stand suture and soon broke open, leading to excessive fluid loss. In addition extraperitoneal closure of an enterostomy or colostomy in an infant is never satisfactory as we are not sure of the size of the lumen at the site of anastomosis, and the thin abdominal wall does not give good cover and leads to kinking of the site of anastomosis (Fig. 3). As post-operative

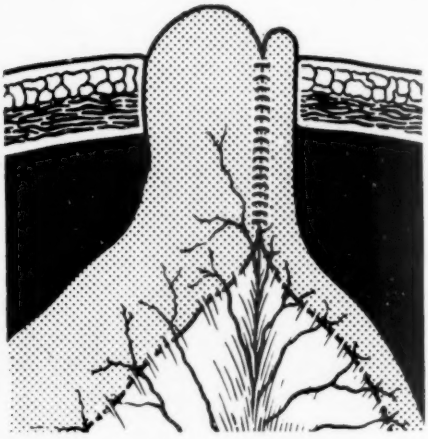


FIG. 3.—Spur colostomy in atresia.

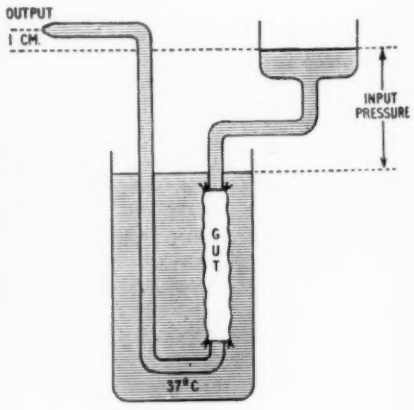


FIG. 4.—Nixon's pump mechanism.

paralytic ileus was mainly responsible for death in cases where bowel appeared to be viable at operation, it was decided that my colleague, Mr. H. Nixon, should carry out research at Great Ormond Street on this problem. He took rabbits, about 3 weeks old, in which the lumen of the small intestine was about equal to that of the neonate. He carried out many forms of anastomosis with an average success of 70%, but in the cases that failed he was never able to produce dilatation and hypertrophy of the proximal end of the bowel. With great ingenuity he then isolated a segment of ileum, reversed it and re-anastomosed it so that the ileum above the proximal anastomosis has become dilated and hypertrophied as seen in the atretic neonate. He then attached lengths of normal and dilated rabbit bowel to a pump mechanism where the outlet could be raised above the inlet and so cause the bowel to transmit fluid against varying pressures. It was noted that rhythmic contractions were present in normal and dilated bowel at normal pressure, but true peristaltic waves

which propel fluid through the pump mechanism were not present in the dilated and hypertrophied bowel until the pressure was raised almost three times as high as that for normal bowel (Fig. 4).

Here lies the explanation of the clinical picture of post-operative paralytic ileus in spite of successful anastomosis. The infant continues to vomit and gastric aspiration has to be maintained. One or two meconium stools may be passed on the second day and then the bowel ceases to function for six to seven days. Attempts to feed through the gastric tube after the passage of the first meconium stool fail, and the only hope is continued intravenous therapy until the dilated bowel can begin to work at normal pressure. It is at this stage that the inexperienced surgeon takes straight X-rays of the abdomen and finds gas and fluid levels still present. He decides that the obstruction has not been relieved and subjects the infant to a further operation.

From Nixon's research work we have learnt that in atresia of the small intestine the proximal dilated and hypertrophied segment must be resected, even though the bowel is viable. The reason for this state of affairs is that in the infant we have not been able to use any form of Miller Abbott tube which would enable us to maintain a head of pressure for the abnormal bowel to act on. Ehrenpreis and Sandblom (1949) have reduced their mortality rate in cases of duodenal atresia from 75% to 25% by forming a gastrostomy and passing a tube into the stomach and through the duodeno-jejunostomy into the efferent loop of jejunum. The dilated segment is rested and the child fed distal to the anastomosis (Fig. 5).

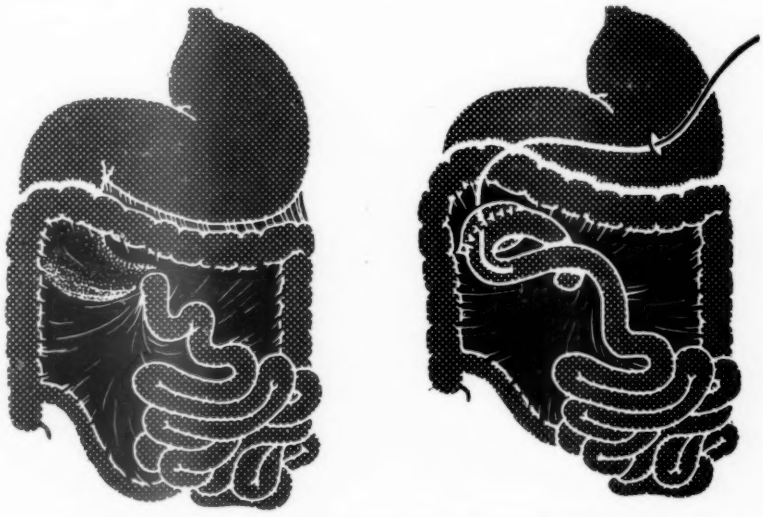


FIG. 5.—Diagram—Gastrostomy and passage of tube through duodeno-jejunostomy.

From the evidence produced it would appear that the treatment for a single area of atresia in the small intestine, is adequate resection of the dilated and hypertrophied proximal blind segment, 25 cm. and more, even though the bowel appears viable, followed by gastrostomy with the passage of a soft rubber catheter into the jejunum so that a head of pressure can be maintained until meconium is passed *per rectum*. Recent figures at Great Ormond Street show that in 15 cases where the proximal distended bowel and atretic area were excised, 10 infants survived, while in 16 cases where the atretic area alone was excised, only 5 infants survived.

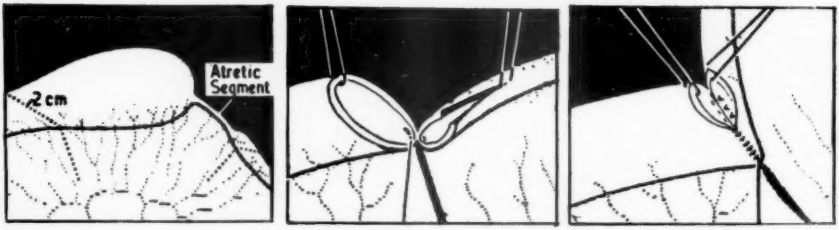
The Anastomosis

A few points of detail about the anastomosis may be of interest at this stage. Not only must there be adequate resection of the proximal segment, but a portion of the distal end must be removed as it usually consists of a fibrous nodule. An oblique incision is made in the proximal segment to provide a lumen of 2 cm. diameter and the oblique incision on the distal segment is carried along its anti-mesenteric border till a 2 cm. diameter is formed. The distal end should be syringed with saline to remove any inspissated meconium that may be present. The anastomosis is carried out by insertion of a single layer of interrupted

silk mattress sutures, and clamps are not used (Fig. 6). Nixon has shown, by experimental work on rabbits, that marked angulation does not cause obstruction and straightens out in about six weeks, and we have proved this to be so in the newborn infant.

The General Problem

Returning to the general problem of intestinal obstruction in the newborn it becomes obvious that the normal passage of meconium is essential to provide a healthy functioning intestinal tract. When are we entitled to expect the passage of the first meconium stool, and when do we note the change to a normal motion? Sticky green meconium should be passed in the first twenty-four hours and by seventy-two hours it disappears and is replaced by small motions, brownish-yellow in colour—provided the infant is being fed—and the normal semi-formed yellow stool is present by the end of the first week. Louw, who analysed our cases at Great Ormond Street, was able to show that 40% of infants suffering from intestinal atresia passed meconium stools, and in duodenal atresia normal meconium stools were passed in 33% of the cases. On the other hand, in Hirschsprung's disease the passage of meconium stools may be delayed for three days. In meconium ileus the meconium is so viscid that it usually does not pass into the large intestine, but obstructs at the lower level of the ileum so that no meconium is passed *per rectum*. The point I would make is that the presence or absence of meconium within the first seventy-two hours of life does not differentiate between complete or partial intestinal obstruction. It was noted in our series of cases that if operation for the relief of complete intestinal obstruction was delayed beyond the third day the proximal distended segment of bowel had usually undergone gangrene or perforation leading to peritonitis. On the other hand, in cases of suspected intestinal obstruction where meconium is passed, it will change in colour and consistency due to the presence of milk curds if the obstruction is incomplete, but again it will take three to four days to do so. In our experience the passage of meconium in the first three days of life by an infant suspected of intestinal obstruction does not provide us with an accurate diagnostic sign. When we look for other clinical signs to confirm the diagnosis of intestinal obstruction we run up against the same degree of inaccuracy.



. . . = Lines of Section. Proximal bowel cut obliquely to give 2 cm. anastomosis. Resection of hypertrophied and dilated terminal bulb—15–25 cm. usually involved.

Inverting mattress suture at mesenteric border. Distal unexpanded bowel cut back along antimesenteric border to equalise length for anastomosis.

3 stay sutures inserted for ease of handling.

One layer inverting mattress sutures inserted along far side of anastomosis, similar layer being inserted along near side.

Completed anastomosis will give about 90° join—"end to back".

FIG. 6.—Treatment of jejuno-ileal atresia by resection and "end to back" anastomosis. Method of anastomosis, Nixon.

Repeated vomiting is a common feature of the condition and is of special diagnostic value if it is bile-stained. Unfortunately, vomiting is often delayed, and the occasional yellow vomit of the normal infant mistaken for a bile-stained vomit. Louw, in analysing our cases showed that the onset of vomiting was delayed for two to three days in 20% of cases of intestinal atresia, and up to two weeks in 50% of cases of intestinal stenosis, where obstruction was incomplete. Dr. G. H. Lathe, at Queen Charlotte's Hospital, has been able to show that the occasional yellow vomit seen in the normal neonate is due to the presence of carotene pigments in the colostrum milk, but the experience of maternity units enables us to state to-day that repeated true bile-stained vomiting associated with failure of passage of meconium in the first three days of life denotes organic obstruction. Once again, we lack a definite clinical sign, for in the analysis of our cases of intestinal atresia, 40% of the lesions were in the duodenum, and of these cases 30% had the level of obstruction proximal to the entrance of the common bile duct, so that the vomit was not coloured by the presence of bile. In cases where the duodenal obstruction is due to the presence of connecti-

tissue bands pressing on the duodenum, associated with failure of rotation of the cæcum, forcible vomiting may be delayed for two weeks, but when it does develop the vomit is often free from bile, and is associated with visible gastric peristalsis so that a diagnosis of pyloric stenosis is made. Failure to palpate a pyloric tumour will indicate further investigation of the case.

We see now that the clinical signs of the passage of meconium and the state of the vomit may lead us astray in diagnosis, so we turn to inspection of the abdomen. The abdomen of the newborn infant tends to be protuberant, so that moderate degrees of distension are easily missed. In 50% of our cases of duodenal obstruction the abdomen appeared normal, and in 50% of cases of intestinal obstruction the abdomen showed only moderate distension. Visible peristalsis was more commonly seen in incomplete lesions than in complete lesions, but even then less than 30% of cases exhibited the sign.

X-ray investigation

The diagnosis is still in doubt in many cases, so we turn to X-ray investigation. Straight X-rays of the abdomen will not harm the infant, and they are taken in the supine or prone and erect positions to show the presence of gas shadows and fluid levels. It will be remembered that air can pass into the colon within the first six hours of life, and the coils of small intestine in the neonate always appear to be dilated. Obstruction of the small intestine cannot be diagnosed unless fluid levels are seen in addition to distended coils of small bowel. The bowel requires to be grossly distended before a fluid level can be seen, and is dependent on the fact that the obstruction has been slowly developing over a period of months. Two conditions will upset the findings; in paralytic ileus due to primary peritonitis the dilated bowel can show fluid levels, and in meconium ileus the meconium may be so viscid that the gas cannot rise above the fluid content to demonstrate the level, but remains imprisoned in the meconium in the form of bubbles of gas. As a provisional diagnosis of primary peritonitis or of meconium ileus justifies laparotomy no great harm has been done to the infant. The point I would make is that by the time fluid levels are present in the small intestine on the X-ray film the obstruction is in an advanced stage, and that where there is only moderate dilatation of the bowel, fluid levels are not easily detected.

Obstruction low down in the colon does not commonly give rise to fluid levels in the small intestine, but we run into the difficulty, that where meconium cannot go, gas cannot go. In Hirschsprung's disease an aganglionic segment may spread up to the splenic flexure or involve the whole colon so that no gas will enter it, and in meconium ileus the viscid meconium plugging the terminal ileum prevents gas entering the colon and may prevent formation of fluid levels in the small intestine. Passage of a rectal tube with a view to colonic lavage to dilate the colon and facilitate the passage of meconium is dangerous, for in Hirschsprung's disease the aganglionic segment of bowel has a weak wall, which is easily perforated.

The presence of gas in the large bowel may be misleading in cases of imperforate anus. Gas will enter the colon within the first six hours of life, but in low obstruction it may not reach the rectum for the first twenty-four hours. Rice's test is used to determine the distance of the blind end of the hind-gut from the perineum and is dependent on gas rising into the pouch on turning the infant upside down. If the X-ray is taken before the first twenty-four hours gas may not have reached the rectum, and if taken at the correct time the X-ray may still be misleading as stagnant inspissated meconium may prevent gas rising into the terminal end of the blind pouch.

Thus there is great variation in the signs of intestinal obstruction in the newborn, which leads to late diagnosis. To add to our difficulties we have the fact that the newborn babe is prepared to live on his own resources for the first few days of life until the maternal flow of milk is truly established, so that unless there is great loss of fluid and electrolytes the general condition of the infant appears to be satisfactory. Sudden deterioration of the infant usually coincides with changes in the bowel wall, for the obstruction has led to distension which causes anoxia, damage to capillaries, outpouring of fluids and electrolytes into the intestine, hæmo-concentration, a failing circulation, and chemical changes causing an unstable respiratory centre leading to periods of apnœa and collapse of the lungs, and weak cough reflex which permits inhalation of gastric content leading to infection of the lungs.

In cases of obstruction of the small intestine, life is not saved by gaining twenty-four hours in the diagnosis, but by preventing sudden fluid and electrolyte loss which is the eruption of the volcano that has simmered as chronic intestinal obstruction for many months.

The following are a few of the difficulties I have encountered in dealing with obstruction at various levels in the intestinal tract:

The diagnosis of duodenal atresia is straightforward if we remember that air passes into

the colon in six hours. Straight X-ray of the abdomen will show air in the stomach and distended duodenal pouch, but none in the small intestine; if doubt arises passage of a gastric tube will remove the air as the pyloric sphincter is incompetent (Fig. 7). Thin barium solution may be used to define the level of obstruction provided it is aspirated following X-ray examination. Duodeno-jejunostomy is the operation of choice, and the passage of a rubber catheter through the anastomosis by way of a gastrostomy is essential to rest the distended duodenum till muscle tone has recovered. At operation the whole of the small intestine is delivered out into the wound and the intestinal tract is searched for other areas of atresia. The fact that there is a high incidence of mongolism associated with duodenal atresia does not prevent my carrying out a life-saving operation.

FIG. 7.—Duodenal atresia. Incompetent pyloric canal. X-ray appearance.

Malrotation of the mid-gut giving rise to connective tissue bands obstructing the duodenum will present as a state of emergency in the neonatal period, or escape notice till late childhood, dependent upon the degree of obstruction set up. If rotation ceases before the mesentery of the small intestine is fixed on a broad base then volvulus of the mid-gut may occur, and its formation cause obstruction at the level of the duodeno-jejunal flexure. Gross, in recent years, has emphasized the presence of these two conditions arising from failure of rotation, for in the neonatal period they may demand laparotomy and the treatment is simple, provided that the bowel is viable (Figs. 8, 9).

I have already dealt with the treatment of atresia of the small intestine, so I would only add that stenosis giving rise to obstruction in the neonatal period must receive the same treatment, and the surgeon should avoid the temptation of carrying out perforation of a single septum through the proximal distended bowel as it will not stand the trauma of incision and closure.

We come now to the rare case of Hirschsprung's disease giving rise to intestinal obstruction in the neonatal period, and find that it may simulate the condition of meconium ileus. In Hirschsprung's disease an aganglionic segment of bowel is present which involves the rectum and sigmoid colon, but may reach as far as the terminal ileum. The aganglionic segment does not possess true peristaltic movement, so delay in the passage of meconium occurs and may lead to intestinal obstruction. Hypertrophy and dilatation of the proximal bowel is a late event, so that abdominal distension associated with marked peristaltic waves is not seen in the neonatal period. Rectal examination usually reveals an undilated rectum which grips the finger, and is followed by the passage of flatus and a few firm pellets of meconium, but if the aganglionic segment is a long one the condition of microcolon will be present and the obstruction may not be relieved. I have seen 5 cases of this type of obstruction and in 2, when a rectal tube was passed in order to wash out the bowel, perfo-

FIG. 8.—Cæcum in mid-line held by bands due to failure of rotation. Divide band and place cæcum to the left. After Ladd and Gross (1941).

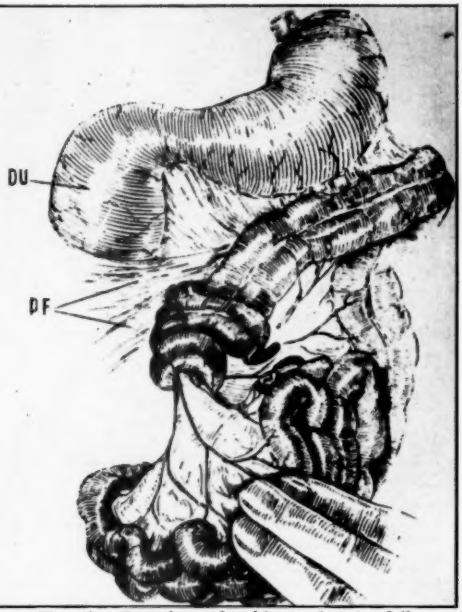


FIG. 9.—Rotation of mid-gut due to failure of mesentery to form attachment on a broad base. Note duodeno-jejunal obstruction as well as band over duodenum. Anti-clockwise rotation reduces the volvulus. After Ladd and Gross (1941).

DU—duodenum. PF—peritoneal fold. SMA—superior mesenteric artery. J—jejunum. C—cæcum.

tion occurred (Fig. 10). I would advise that if rectal examination will not relieve the condition and obstruction is threatening life then laparotomy should be carried out. On opening the abdomen the aganglionic segment appears to be atretic and if the whole of the colon is involved, the dilated terminal ileum will be blocked with meconium and taper in cone fashion to the cæcum. In meconium ileus the viscid meconium blocking the terminal ileum will present the same picture, but doubt is soon resolved on aspiration of the bowel content, as in Hirschsprung's disease the meconium is in a fluid state.

What then should we do if we run across acute intestinal obstruction in the neonatal period in Hirschsprung's disease? If rectal examination is of no avail then we are forced to carry out laparotomy. Fortunately, the aganglionic segment does not usually extend beyond the splenic flexure so transverse colostomy will suffice. Laparotomy will only show early dilatation so that coning to the aganglionic segment is indistinct; so the change should be marked with a silk ligature well proximal to the cone and a section of bowel wall taken for microscopy. It is our best chance of finding the true level of pathological change, even though we have frozen-section technique to help us when we come to remove the aganglionic segment. In 2 cases where a life-saving transverse colostomy has been carried out, I have run up against the difficulty of the distal segment failing to dilate, with the result that the blood vessels to the distal colon have not elongated, so that mobilization after excision of the affected segment cannot be carried out. To-day we can anastomose ileum to anal canal so our duty in the neonatal period is to save the life of the infant. Biopsy of the submucous coat of the rectum will reveal the aganglionic segment, but in face of acute intestinal obstruction in the neonatal period it will not alter procedure.

What of meconium ileus? All cases at Great Ormond Street Hospital operated on died until 1950, when a case under my care was operated on by Nixon. He found the terminal distended loop of ileum rotated on itself and impending gangrene present. He reduced the volvulus, and fixed the loop by enterostomy to the anterior abdominal wall. Repeated washouts with pancreatin solution, and administration of pancreatin granules by mouth caused the meconium to gain a fluid state, and the obstruction was relieved. Two attempts at closure of the ileostomy failed, so it was decided to leave it alone, on the principle that

FIG. 10.—Perforation of sigmoid colon by rectal tube.

once the normal channel is acting the abnormal will close. In this case we were successful. Since that date, Bodian's monograph "Fibrocystic Disease of the Pancreas" has been published, with the result that early forms of the disease have been diagnosed and true cases of meconium ileus have responded to resection of the small intestine involved. Involvement of the lungs by viscid mucus leading to infection is the usual cause of death, but we have now learnt that meconium ileus may be present in some cases without severe lung complications, and that the use of antibiotics can keep the lungs free from infection, and the administration of pancreatin by mouth will replace the lack of tryptic activity.

Imperforate Anus

In the treatment of this condition we do not lose life but are faced with poor functional results. Where there is malformation of rectum and anal canal about 50% of the cases have fistulous communication with the genito-urinary tract. In these cases there are very few but definite indications for perineal approach to relieve the obstruction. These indications are as follows:

In the male there must be true evidence of a proctodeum with a bulging membrane, or a triangular portion of skin present covering the true anal canal (Figs. 11, 12). The presence of dimpling of the anal raphe on cutaneous stimulation is due to contraction of the external sphincter muscle. As the development of the muscle is not dependent on the presence of terminal bowel, dimpling does not denote the near presence of distended hind-gut. If the two conditions mentioned are not present in the male, the blind end of the hind-gut usually lies on the abdominal surface of the levator ani muscle, and operation by the perineal route will not be successful.

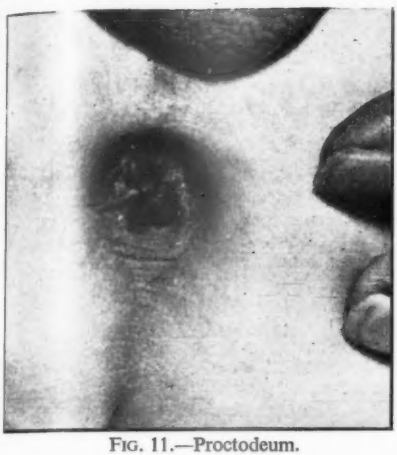


FIG. 11.—Proctodeum.

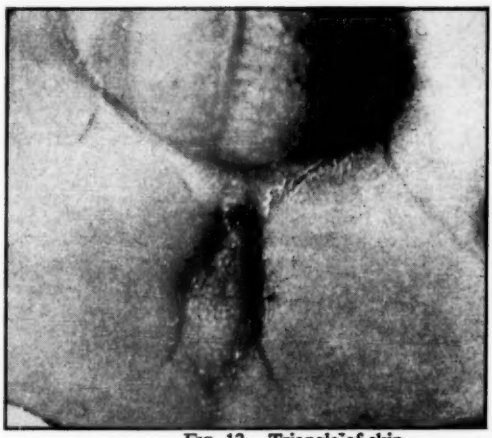


FIG. 12.—Triangle of skin.

Perineo-abdominal operation has been advised on the first day of life and can be carried out, but I find that we get poor functional results. I advise laparotomy exposure and definition of the blind end of the distended hind-gut, for 50% of cases have a communication with the prostatic urethra. I double-ligate and divide the communication if present, so that the renal tract is freed from infection. I proceed to a life-saving transverse colostomy, and at the age of 18 months mobilize the blind end and pass it through the pubo-rectalis sling of fibres of the levator ani muscle, keeping close to the back of the prostate gland. Rectal mucosa must be redundant, and the new anal canal must be placed in an anterior position so that the pubo-rectalis sling embraces it and ensures continence.

In the female, a great advance has been made in rectal surgery of childhood by recognition of the communication between rectum and lower vagina or vulva. Obstruction may be present in the neonatal period, but does not usually occur until solids are introduced into the feeds. Denis Browne has called this condition "ectopic anus", others a fistulous communication. The main point to recognize is that the anal canal has turned forwards from its true position and that the opening is abnormally small. Browne's cut-back operation restores the common opening for vagina and rectum as seen in the cloacal stage, but as the new rectum straightens out the posterior vaginal wall will reform and the two openings will be reconstituted. Here again the important point is not to place the rectum in the hollow of the sacrum, but to see that the cut-back provides a new anal canal placed in an anterior position and embraced by the pubo-rectalis sling of muscle fibres.

As a surgeon, these are my ideas on the principles to be employed in the treatment of intestinal obstruction of the newborn, but we must remember the role of the anæsthetist and the biochemist. Intratracheal anæsthesia is essential to provide a free airway in the presence of an unstable respiratory centre, and to prevent inhalation of gastric content. Scoline as a muscle relaxant is safe to use in such infants, and is of great assistance to the surgeon.

In all cases of high intestinal obstruction in the neonatal period, intravenous therapy as a pre-operative resuscitative measure is required, and will need to be continued into the post-operative period for several days. Laboratory techniques will be required to assess the ever-changing state of alkalosis, acidosis, and ketosis, so that the biochemist becomes a member of the team in dealing with these problems. Antibiotics to combat peritonitis are best administered by intramuscular injection.

From my own experience, I would suggest that the solution of these problems of congenital malformation lies more in a greater understanding of the varying states of pregnancy, than in the pursuit of surgery.

REFERENCES

BODIAN, MARTIN (1952) Monograph—Fibrocystic Disease of the Pancreas. London.

EHRENPREIS, T. L., and SANDBLOM, P. (1949) *Acta pædiat. Stockh.*, **38**, 109.

GROSS, R. E. (1953) The Surgery of Infancy and Childhood. Philadelphia, p. 192.

LAPP, W. E., and GROSS, R. E. (1941) Abdominal Surgery of Infancy and Childhood. Philadelphia, p. 64.

LOUW, J. H. (1952) *S. Afr. J. clin. Sci.*, **3**, 109.

NIXON, H. H. (1954) Experimental anastomoses in rabbits. Personal communication.

WANGENSTEEN, O. H., and RICE, C. O. (1930) *Ann. Surg.* **92**, 77.

BOOKS RECEIVED FOR REVIEW

Bannister (K.), *et al.* Social case work in marital problems: the development of a psychodynamic approach. pp. xii + 199. London: Tavistock Publications. 15s. 0d. 1955.

Blond (K.). The liver and cancer: a new cancer theory. pp. x + 220. Bristol: John Wright. 27s. 6d. 1955.

Burton (A. C.), and Edholm (O. G.). Man in a cold environment: physiological and pathological effects of exposure to low temperatures. pp. xiv + 273. London: Arnold. 30s. 0d. 1955.

Current Work in the History of Medicine. No. 3, July–September 1954. pp. 81–123. London: Wellcome Historical Medical Library. 1954.

Gaisford (W.), and Lightwood (R.), eds. Pædiatrics for the practitioner. 3 vols. and index London: Butterworth. £13 10s. 0d. per set. 1953–55.

Harrison (R. G.), ed. Studies on fertility. Including papers read at the Conference of the Society for the Study of Fertility, London, 1954. Being Volume VI of the Proceedings of the Society. pp. ix + 151. Oxford: Blackwell. 21s. 0d. 1954.

Hughes (Brodie). The visual fields. pp. ix + 174. Oxford: Blackwell. 35s. 0d. 1954.

MacNalty (Sir Arthur S.), ed. The civilian health and medical services. (History of the Second World War, United Kingdom Medical Series.) Vol. **2.** pp. xi + 406. London: H.M.S.O. 45s. 0d. 1955.

Major (R. H.). A history of medicine. 2 vols. Oxford: Blackwell. £5 5s. 0d. 1954.

Sebrell (W. H., Jr.), and Harris (R. S.), eds. The vitamins: chemistry, physiology, pathology. 3 vols. New York: Academic Press. Vol. **1:** $16.50; Vol. **2:** $16.50; Vol. **3:** $15.00. 1954.

Stokes (E. J.). Clinical bacteriology. pp. vii + 288. London: Arnold. 20s. 0d. 1955.

Wilson (S. A. Kinnier). Neurology. Edited by A. Ninian Bruce. 2nd edit. 3 vols. London: Butterworth. £10 10s. 0d. per set; £3 10s. 0d. per volume. 1954–55.

BOOKS RECENTLY PRESENTED AND PLACED IN THE SOCIETY'S LIBRARY

Angela (G. C.), *et al.* Moderni aspetti della terapia della colite ulcerosa. pp. 158. Pisa: Omnia Medica. 1953.

Aveling (F.). Personality and will. pp. 245. London: Nisbet. 5s. 0d. 1931.

Botman (J. W. M.). Over verlammingen van de nervus facialis van intratemporale oorsprong. 's-Gravenhage: Uitgeverij Excelsior. 1954.

Bridges (K. M. B.). The social and emotional development of the pre-school child. pp. 277. London: Kegan Paul. 12s. 6d. 1931.

Chaslin (P.). Éléments de sémiologie et clinique mentales. p. 956. Paris: Asselin et Houzeau. 1912.

Congresses. Dermatology. Proceedings of the 10th International Congress of Dermatology, London, 1952. pp. 552. London: British Medical Association. 1953.

Congresses. Physiology. 19th International Physiological Congress, Montreal, 1953. Abstracts of communications. pp. 976. Montreal. 1953.

Congresses. Physiotherapy. Proceedings of the (7th) International Congress of Physical Medicine, London, July 1952. pp. 344. London: Headley. 1955.

Crocker (H. R.). Diseases of the skin: their description, pathology, diagnosis and treatment with special reference to the skin eruptions of children and an analysis of fifteen thousand cases of skin disease. 3rd edit. 2 vols. London: Lewis. 1903.

(*continued on page 32*)

Section of Endocrinology

President—P. M. F. BISHOP, D.M., M.R.C.P.

[*November* 24, 1954]

Hypopituitarism with Slipped Femoral Epiphysis.—IVOR H. MILLS, M.B., M.R.C.P. (for Professor F. T. G. PRUNTY, M.D., F.R.C.P.).

The patient was a man aged 28. At the age of 7 he fell on his head. He was not unconscious and was apparently normal immediately afterwards. About three months later he started getting headaches and was admitted to Willesden Hospital and later to Queen Mary's Children's Hospital. No details of these investigations are available except that a lumbar puncture was performed. Altogether he was away from school for eighteen months. This did not affect him appreciably because he did well and left from the top class aged 14.

Three years ago (aged 25) he slipped and fell on his left hip. He was quite well afterwards for two months. Then he started to limp and had pain in the left thigh. He noticed his left leg was shorter than the right. At St. Helier's Hospital a diagnosis of slipped left femoral epiphysis was made and in March 1952 a Smith-Petersen pin was inserted. He returned to work for a year, until in April 1953 pain recurred in the left hip and the pin was removed. A diagnosis of hypopituitarism was then made.

On admission to St. Thomas's Hospital in May 1953 he had rather an "old-age" look with smooth, pale facial skin. His height was 5 ft. 6 in. and span 5 ft. 5 in. and weight 6 st. 11 lb. His voice was unbroken and he had no axillary, chest or pubic hair. The external genitalia were undeveloped but two small testes were in the scrotum.

His blood pressure was 100/60 mm.Hg. There was no abnormality in the central nervous system, in particular his fundi were normal and visual fields full.

Demonstration showed the typical signs of left slipped femoral epiphysis and a voice which, though broken, was still not very deep.

X-ray of left hip and the slipped epiphysis are shown in Fig. 1A (May, 1953).

The open epiphyses at the wrist and X-ray of the sella turcica are shown in Fig. 2. In the latter the sella is definitely enlarged.

A B

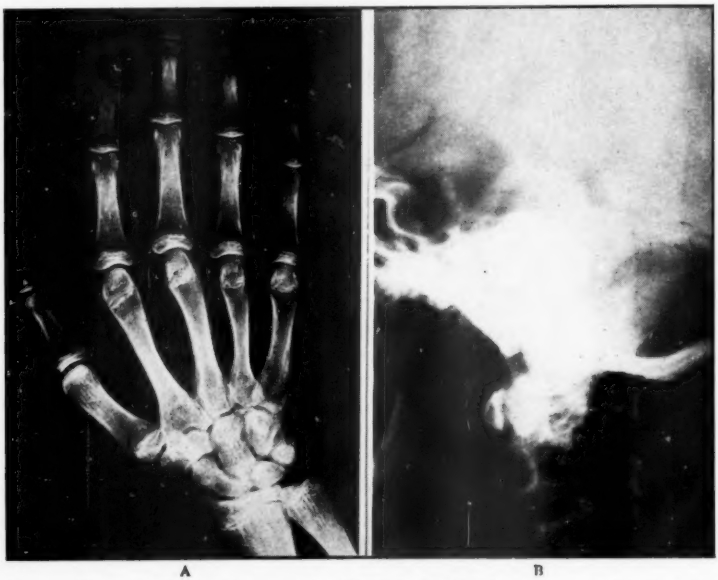
FIG 1.—(A), Slipped epiphysis after the Smith-Petersen pin had been removed in May 1953. (B), Fusion of the epiphysis following treatment, in October 1954.

The blood W.R. and Kahn tests were negative.

The urinary F.S.H. on three occasions was less than 4 mouse units per day.

The testicular biopsy (Fig. 3) shows a pattern which is compatible with hypopituitarism. The tubules have developed from the pre-puberal stage but no spermatozoa are being formed, a few spermatocytes only being present; some of the Sertoli cells have rather foamy cytoplasm and there is thickening of the basement membrane. Leydig cells are practically

absent. These facts are in keeping with the testis having had some gonadotrophic stimulation but having subsequently regressed.



A B

FIG. 2.—(A), Open epiphysis of the wrist. (B) Part of the lateral view of the skull showing the enlarged sella turcica.

FIG. 3.—Section of the testicular biopsy showing the open lumina, arrested spermatogenesis, the relatively normal Sertoli cells, some with foamy cytoplasm, thickening of the basement membrane and the virtual absence of Leydig cells. ×110.

The B.M.R. was −38% and the glucose tolerance test was normal. The insulin sensitivity test was carried out with half the standard amount of insulin. The blood sugar values at times 0, 20, 30, 45, 60 and 90 min. were 92, 63, 42, 60, 75, 102 mg.%. These show increased sensitivity to insulin. The Kepler test was positive; night volume = 493 ml., largest day volume = 22 ml., and factor = 1. His plasma sodium was 123 mEq./l. and potassium 4·5 mEq./l. Urinary 17-ketosteroids ranged between 0·52 and 1·9 mg. per twenty-four hours. He showed considerable resistance to ACTH and his steroids even with intravenous infusion, 20 units per day for five days, rose only to 4 mg. per twenty-four hours. His eosinophils fell from 200 to 20/c.mm.

The clinical response was far greater than the biochemical one and he became much livelier. Treatment with ACTH gel 10 units daily was continued.

A month later testosterone therapy was begun; at first with testosterone phenyl propionate and later with testosterone propionate. The equivalent of 5·4 grams of testosterone was given over five months and then 500 mg. was implanted. Thyroid was given from three weeks after the testosterone and worked up to 1 grain, twice daily. All three forms of treatment have been continued for fifteen months and the epiphyses are now fused (Fig. 1B).

The cause of the hypopituitarism is not definite. It seems very unlikely that the accident at the age of 7 had anything to do with it because he continued to grow and develop and the testis biopsy shows puberty changes.

The enlarged sella turcica suggests destruction of the pituitary by a tumour and although there is no other evidence of a tumour this is the most likely diagnosis and that the pituitary destruction occurred at about the time of puberty.

The point of greatest interest in this case is the slipping of the femoral epiphysis. Pituitary dwarfs have open epiphyses but they do not usually slip. Most cases of hypopituitarism have their onset after the epiphyses have fused.

Normally slipped epiphysis occurs in children between the ages of 10 and 16 years, who may be divided into two groups: the short and fat, and the tall and thin.

Harris (1950) carried out some interesting experiments on the cause of the slipping. Working with hypophysectomized rats he measured the shearing force required to move the tibial epiphysis. The rats were divided into groups which were treated with (1) growth hormone, (2) œstrogens, (3) testosterone. The force required to move the epiphysis was least in the growth-hormone-treated group and most in those given œstrogen. Testosterone had a similar effect to œstrogen, if given in large doses for a long time. Harris correlated his results with the histology in each case. The zone of hypertrophied cartilage cells, where the matrix is least, is widest under growth hormone and least under œstrogen.

He suggested that slipping of the epiphysis is determined by the ratio of growth hormone to sex hormone. This, he thinks, correlates with the two clinical groups, the first with normal growth hormone but low sex hormone and the second with high growth hormone but normal sex hormone. In each case the ratio is raised.

Dr. Raymond Greene (1954) showed a case of a man with open epiphyses who continued to grow with implants of testosterone of 400 mg. and, later, of 1 gram but who, with combined testosterone and œstrogen implants, ceased growing and the epiphyses closed.

One other factor has to be taken into account and that is the effect of thyroid hormone. Ray *et al.* (1954) have shown in hypophysectomized, thyroidectomized rats that while growth hormone has no effect on skeletal maturation thyroid does have an effect.

In the present case testosterone was given in large doses for six months and thyroid was given as well. Both these hormones would help the closure of the epiphyses which the X-rays demonstrate.

REFERENCES

GREENE, R. (1954) *Proc. R. Soc. Med.*, **47**, 446.
HARRIS, W. R. (1950) *J. Bone Jt. Surg.*, **32B**, 5.
RAY, R. D., ASLING, C. W., WALKER, D. G., SIMPSON, M. E., LI, C. H., and EVANS, H. M. (1954) *J. Bone Jt. Surg.*, **36A**, 94.

Mr. Pickering Pick: We removed a Smith-Petersen pin from Dr. Mills' patient. In our experience two clinical types of patient are seen with slipped epiphyses, the short fat ones and the tall thin ones, and this fits in well with Harris's paper referred to by Dr. Mills. It is possible to diagnose the very early slip clinically and we are getting better at doing this. It would therefore be a great advantage if the endocrinologist could fuse the epiphysis by other therapy rather than the somewhat blunderbuss method of inserting a metal nail. Although from time to time their help in the matter has been requested, I understand that there are considerable difficulties.

Dr. A. Stuart Mason: I have recently seen a patient aged 14 who at the age of 8 had a craniopharyngioma explored and partially removed. She showed definite signs of mild hypopituitarism associated with diabetes insipidus. At the age of 13 she developed a slipped femoral epiphysis which was treated with a Smith-Petersen pin. Unfortunately avascular necrosis resulted. She was definitely obese but short for her age.

Dr. Mills: Eunuchs are the extreme case of a high growth-hormone to sex-hormone ratio. I do not think that œstrogen acts by suppressing growth hormone. Although Harris suggests this in his paper, some of us do not believe it and I think it is more probable that the œstrogen has a direct action.

Adrenocortical Hyperfunction associated with Hirsutism, Obesity, Hypertension and Normal Glucocorticoid Secretion.—OLIVER GARROD, M.D., M.R.C.P., and A. E. KELLIE,[1] Ph.D.

S. C. (Middlesex Hosp. No. H: 67258), a student of 18, born of Russian parents, developed normally until the menarche at 12, which was followed closely by the onset of obesity. Menses were normal for the first six months, but have since been scanty and very infrequent. For two years there has been increasing hirsutism of the chin, trunk and limbs. Otherwise her health has been good and has not prevented her from playing games at school. There is no known obesity, hirsutism or endocrine dysfunction in her family.

On examination (August 1954).—Sensible girl with a feminine psyche. Healthy skin, free from striæ, purpura or acne. "Buffalo" obesity, sparing limbs, weight 12 st. 8 lb. (80 kg.), height 5 ft. 2 in. Marked hirsutism of chin, moderate hirsutism of body and limbs, with pubic hair extending to umbilicus. Larynx, clitoris, muscles and skeleton normal. Labile hypertension, ranging between 185/120 and 120/75 mm.Hg. Abdominal and rectal examinations negative. Urinalysis normal.

Investigations.—General: Hæmoglobin 13·3 grams% (92%); W.B.C. 4,800/c.mm. Chest X-ray, skull X-rays, intravenous pyelography and skeletal X-rays normal.

Endocrine: (1) Adrenal cortex. (*a*) Glucocorticoid functions: Blood eosinophils, 768 and 376/c.mm. Glucose tolerance test (standard): 0 min., 108; 30 min. 112; 60 min., 104; 120 min., 108 mg.%. Plasma hydrocortisone: 3·1 μg./100 ml. (normal). Urinary 17-hydroxycorticoids: 7 and 10 mg./twenty-four hours (normal).

(*b*) Mineralocorticoid functions: Plasma sodium 142, potassium 4·0, chloride 100, CO_2 29 mEq./l.; total body water (urea method) 60%; Plasma aldosterone concentration not raised.

(*c*) Androgenic functions: Urinary 17-ketosteroid excretion 30, 31 and 32 mg./twenty-four hours, falling during cortisone suppression test to 6·8 mg. (Fig. 1). Patterson's test

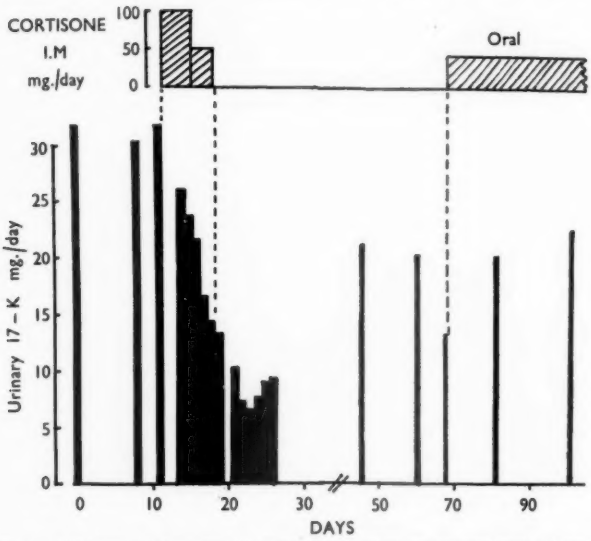


FIG. 1.—Urinary 17-ketosteroid excretion in relation to cortisone therapy.

for dehydro*iso*androsterone (D.H.A.) negative. Differential analysis of urinary 17-ketosteroids by column chromatography showed D.H.A. excretion of 7·7 mg./day, falling to 0·5 mg. during cortisone suppression test (Fig. 2) (normal range 0·5–3·5 mg./day).

(2) Urinary pregnanediol, 1·7 mg./twenty-four hours (normal).

(3) Basal metabolic rate −1%.

Subsequent progress.—The patient lost 14 lb. during one month in hospital on a reducing diet. Since discharge from hospital the weight has remained steady and the blood pressure normal. Urinary 17-ketosteroid excretion returned to about 20 mg./day and did not fall

[1]Intermediate Fellow of the British Empire Cancer Campaign.

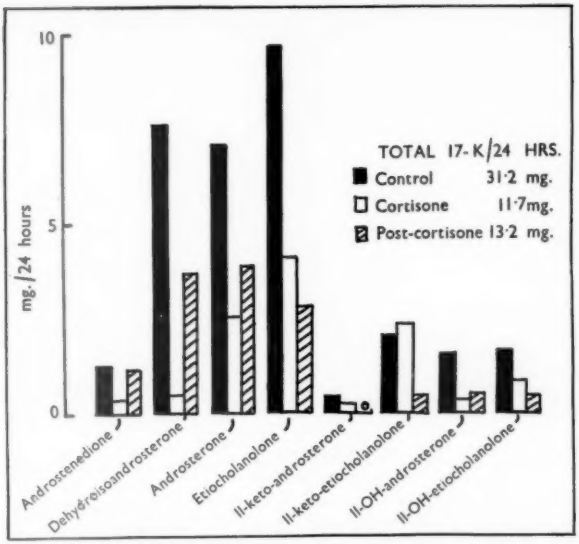


FIG. 2.—Differential analysis of urinary 17-ketosteroid excretion before, during, and fifty days after suppression by intramuscular cortisone (*see* Fig.1).

further during six weeks on oral cortisone (12·5 mg. eight-hourly) (Fig. 1). Urinary D.H.A. excretion returned to 3·8 mg./day. Normal menses have returned.

Comments.—(1) *Diagnosis:* Cushing's syndrome was excluded by finding normal glucocorticoid function, and adrenogenital syndrome by the absence of virilism, though distinction between the latter syndrome and adrenal hirsutism may be only a matter of degree. The high output of 17-ketosteroids, including D.H.A., indicates adrenocortical hyperfunction, which is presumably the cause of the hirsutism. The marked suppression of 17-ketosteroid and D.H.A. excretion by cortisone probably excludes an adrenal or ovarian tumour (Jailer *et al.*, 1954).

Hirsutism, obesity, and amenorrhœa or oligomenorrhœa, are often associated with polycystic ovaries (Stein and Leventhal, 1935; Buxton and van der Wiele, 1954). However, excessive 17-ketosteroid excretion, and suppression of 17-ketosteroid excretion by cortisone, appear to be exceptional in the Stein-Leventhal syndrome (Buxton and van der Wiele, 1954; van der Wiele *et al.*, 1954) though occasionally adrenocortical hyperfunction may be associated with this condition (Abu-Haydar *et al.*, 1954). This possibility cannot be excluded in the present case without surgical exploration.

The hypertension and obesity, though their significance is not clear, may be due to oversecretion of unidentified adrenal steroids, but evidently not to 17-hydroxycorticoids or aldosterone, which were not present in excessive amounts.

(2) *Treatment:* Surgical intervention with a view to subtotal adrenalectomy and exploration of the ovaries was felt to be unjustifiable in the absence of virilism and sustained hypertension. This attitude has been confirmed by the partial remission following the cortisone suppression test, but may need revision according to the further clinical course. It has not been possible to reduce 17-ketosteroid excretion further with physiological doses (37·5 mg. a day) of oral cortisone. This therapy is being withdrawn.

ACKNOWLEDGMENT

Our thanks are due to Professor A. Kekwick for allowing us to study this patient under his care.

REFERENCES

ABU-HAYDAR, N., LAIDLAW, J. C., NUSIMOVICH, B., and STURGIS, S. (1954) *J. clin. Endocrin.*, **14**, 766.
BUXTON, C. L. and VAN DER WIELE, R. (1954) *New Engl. J. Med.*, **251**, 293.
JAILER, J. W., GOLD, J. J., and WALLACE, E. Z. (1954) *Amer. J. Med.*, **16**, 340.
STEIN, I. F. and LEVENTHAL, M. L. (1935) *Amer. J. Obstet. Gynec.*, **29**, 181.
VAN DER WIELE, R., JAILER, J. W., GOLD, J. J., and LIEBERMAN, S. (1954) *J. clin. Endocrin.*, **14**, 776.

Dr. A. E. Kellie: We have recently applied gradient elution chromatography for the differential analysis of total urinary 17-ketosteroid fractions. When applied to the present case this procedure showed that the absolute amounts of all 17-ketosteroids were increased and were above or in the high normal range. As all components were increased the percentage composition of the fraction was similar to that found in normal cases except with respect to the D.H.A. which was present in amounts significantly above normal.

The pattern of excretion was unlike those which we have obtained from two cases of Cushing's syndrome.

On treatment with cortisone all components fell, with the exception of C_{11}-oxygenated etiocholanolone derivatives which are cortisone metabolites. The decrease in D.H.A. was very striking and appeared to be selective.

The Webbing Syndrome (Ullrich-Turner) With and Without Gonadal Agenesis. Chromosomal Sex Typing by Skin Cell or Leucocyte Examination in Diagnosis.—ALEX. RUSSELL, O.B.E., M.D., M.R.C.P., B. LEVIN, M.D., Ph.D., and N. E. FRANCE, M.B., B.Ch. (for MARY WILMERS, M.D., F.R.C.P.).

Case I.—P. B. Referred at 11½ years of age by Dr. A. Essex-Cater as Turner's syndrome. No hereditary traits traceable.

Typical pattern of syndrome except for absence of cubitus valgus:

Gross bilateral webbing of neck (right side already corrected by plastic surgery: Mr. R. Battle) and slight submental webbing. Low hair-line posteriorly with lateral extensions. Stunting of growth (Height 53·0 in., i.e. 5·3 in. < 50th percentile level). Bone age 11–12 years.

Also facial stigmata, including low-set ears, down-drawn angles of mouth and receding jaw. Small inverted nipples and genitalia suggested no more than infantile status of sexual development.

Rectal examination.—Cervix palpable. C.V.S.: N.A.D. B.P. 120/80.

Investigations.—Vaginal: pH alkaline. Smear: Numerous superficial cells with evidence of early œstrogenization compatible with age.

Urinary F.S.H.: < 5 m.u.

17-ketosteroid excretion: 3·6 mg./twenty-four hours.

One year later (aged 12½ years): No significant alteration in vaginal pH smear, F.S.H. assay, or clinical appearance.

Chromosomal sex typing: (*a*) Skin biopsy (Moore *et al.*, 1953; Hunter *et al.*, 1954): Female. (*b*) Leucocyte examination (Davidson and Robertson-Smith, 1954): Female.

Provisional diagnosis: Webbing syndrome with ovaries present.

Laparotomy (Mr. Valentine Swain): Ovaries present bilaterally, each showing several follicular cysts.

Case II.—A. L. Presented as growth-failure. Referred aged 13 7/12 years as "Ullrich-Turner syndrome. ? Ovarian agenesis" by Dr. Mary Wilmers. Father and mother small (5 ft. 4 in. and 5 ft. 2 in. respectively). No other hereditary traits definable.

Typical pattern of syndrome: Slight neck webbing with low hair-line posteriorly.

Stunting of growth (height 52·6 in.: approx. 10·0 in. < 50th percentile, but bone age normal, viz. 13 years). Broad shield-like chest with widely spaced nipples and depressed sternum. Cubitus valgus (carrying-angle = approx. 30 degrees). Also bilateral digital anomalies, viz. shortening of 4th and 5th fingers due to malformation of 4th and 5th metacarpals, hyperflexibility of many joints, and residuum of lymphangiectatic œdema of right hand (a common accompaniment of the basic syndrome, more prominent in infancy), now only appearing intermittently.

Status of secondary sexual development.—Small inverted nipples with small unpigmented areolæ, and genitalia suggested infantile status.

Rectal examination.—Small cervix palpated. C.V.S.: N.A.D. Blood pressure 130/85.

Investigations.—Vaginal: pH alkaline. Smear: moderate numbers of cornified cells indicative of early œstrogenization.

17-K.S.: 4·25 mg./twenty-four hours. Urinary F.S.H.: 5 m.u. Serum calcium (estimated in view of brachydactyly recalling pseudo-hypoparathyroidism) = 10·2 mg.%.

Chromosomal sex typing: (*a*) Skin biopsy: male; (*b*) Leucocyte examination: male.

Provisional diagnosis: The webbing syndrome with gonadal agenesis. Since a cervix was palpable, fully feminized male intersexuality with testes was excluded, but still remote possibility of "true" (gonadal) intersexuality.

Laparotomy (Mr. Valentine Swain): Hypoplastic uterus and adnexæ present. Bilateral narrow elongated fibrous cords attached to broad ligaments typifying the rudimentary "ovaries" of so-called ovarian agenesis, but presumably rudimentary testes.

Histology: Groups of cells resembling ovarian hilus cells or Leydig cells in an ovarian type stroma.

Comment.—These two examples of the basic webbing syndrome, one with, the other without, gonadal agenesis, are presented in illustration of:

(1) The misleading implication of the label "Turner's syndrome" that sexual infantilism is inevitable in female subjects of neck webbing. This only obtains in the minority: in only about one-third of all recorded cases has there been evidence of primary gonadal deficiency (Rossi and Caflisch, 1951).

Confusion could be averted by a less equivocal title for the basic syndrome (as first codified by Ullrich, 1930, and later by Rossi and Caflisch, 1951), such as "the webbing syndrome", only adding "with gonadal agenesis" when this is proven.

(2) Frequently misleading clinical and laboratory criteria of secondary sexual development in such cases until well into their 'teens.

In *Case II*, apparently "moderate" œstrogenization of the vaginal smear together with low urinary F.S.H. excretion at the age of 14 years pointed to the presence of ovaries. But this was questioned after chromosomal sex typing (male), and then firmly refuted at laparotomy. In subjects of the webbing syndrome, even when puberal development is lacking in their late 'teens, one cannot presume gonadal agenesis. In the case presented by Lovel (1952), the patient's mother, who also showed gross neck webbing, had not menstruated until her 19th year, and never developed pubic or axillary hair, whilst the mother of Varney *et al.'s* first case (1942) showed immaturity of breast development and postponement of menarche until her 20th year.

(3) The application of chromosomal sex-typing techniques to the early clarification of this diagnostic issue is in turn dependent upon the significance of male chromosomal typing in relation to the histology of the rudimentary gonad and to other characteristics displayed by both Case II and the example of "ovarian agenesis" presented to this Section in 1952 (Russell and Swyer, 1952). In the course of this presentation the possibility of male genetic sex was raised on the following histological and embryological grounds.

With failure of the primordial germ cells to penetrate the cortex of the primitive gonadal anlage, or their early annihilation therein, sex maturation of the gonads is aborted (Witschi, 1951). Although, as we observed in 1952, "cortical elements specific to the sex of the gonad would then not emerge . . . medullary rudiments (derived from mesonephric blastema invading via the gonadal hilum) should be relatively unaffected, thus persisting as in this and other like cases". Thus we had described "prominent clumps of 'hilus' cells, large pale-staining polygonal cells disposed along the course of nerves and *strongly resembling Leydig cells of the testes*"—a description equally applicable to the rudimentary gonad in Case II.

Male chromosomal typing in both cases now imparts special force to this analogy, the rudimentary gonads being almost certainly testicular rather than ovarian.

However, in the event of such early interruption of testicular maturation subsequent feminization may find an explanation in the "prenatal castration" studies of Jost (1947) in rabbits, and of Raynaud and Frilley (1947) in mice. Embryos in whom Jost had transplanted the gonads before their vital penetration by primordial germ cells, invariably differentiated in a female direction irrespective of their predetermined genetic sex. It is thus tempting to hold up examples of gonadal agenesis as the *human* counterparts of these prenatal castrates, feminization ensuing in the absence of embryonic testicular androgens by virtue of either basic genetic "drives", or more probably of unrestrained maternal œstrogenization. Another clinical phenomenon, however, detracts from this otherwise attractive hypothesis: the appearance of unequivocally masculinized infants despite bilateral testicular agenesis. Only evidence that "agenesis" in such cases is in reality the end-product of destructive lesions at a much later stage of fœtal life could counter this broadside.

Two other points emphasized in the discussion at the same time (Russell and Swyer, 1952) now also acquire enhanced significance:

(*a*) That the "clitoric hypertrophy" noted in this case—an observation recorded in this syndrome on only one previous occasion (Pich, 1937)—might be a subtle token of male intersexuality.

(*b*) That the commonest cardiac anomaly in these cases—coarctation of the aorta—is predominantly a lesion of males, by 8 : 1 according to Lewis (1933).

Confirmation of such speculation only became possible with the advent of chromosomal sex typing by means of Moore *et al.'s* skin biopsy technique (1953), and later by the even more startlingly simple neutrophil leucocyte criteria of Davidson and Robertson-Smith (1954), both techniques being exploited in our study of these and other cases.

It would now appear that in most cases of so-called ovarian agenesis linked to the

webbing syndrome we are, in reality, dealing with a distinctive form of male intersexuality in which the gonads are neutralized, and the genital system completely feminized with the exception of apparent "clitoric hypertrophy" in some cases, or even true prostatic remnants as in Pich's case.

Diagnosis

From the practical standpoint of clinical diagnosis, male chromosomal criteria in a "female" subject of the webbing syndrome, whilst of value in at once establishing the absence of bilateral ovaries, do not necessarily prove the existence of testicular "agenesis". They may also betoken the rare possibility of fully externally feminized male intersexuality *with testes*, or even "true" (gonadal) intersexuality, being linked with the webbing syndrome. Male intersexuality of this type would be indicated by externally definable gonads or by failure to palpate the cervix on rectal examination, or to see it in the vault of the rudimentary vaginal pouch.

Where the sex chromosomal criteria prove to be *female*, it remains probable, although we have failed to substantiate this in three examples, that gonadal agenesis may still obtain, although this time superimposed upon a genetic female. For example, Wilkins *et al.* (1954) referred to 2 cases of "ovarian agenesis" as demonstrating female chromosomal sex on skin biopsy. Even if this does apply in female subjects of the webbing syndrome, chromosomal sex typing would still provide one exceedingly simple screening device for gonadal status in such cases, of especial value before their late 'teens when criteria other than those exposed at laparotomy are often contradictory.

A fuller discussion of this aspect of the subject in relation to a larger series of the webbing syndrome, with and without gonadal agenesis, is to be published elsewhere.

References

Davidson, W. M., and Robertson-Smith, D. (1954) *Brit. med. J.*, i, 1379.
Hunter, W. F., Lennox, B., and Pearson, M. G. (1954) *Lancet*, i, 372.
Jost, A. (1947) *C.R. Soc. Biol. Paris*, **141**, 126.
Lewis, T. (1933) *Heart*, **16**, 205.
Lovel, K. (1952) *Proc. R. Soc. Med.*, **45**, 589.
Moore, K. L., Graham, M. A., and Barr, M. L. (1953) *Surg. Gynec. Obstet.*, **96**, 641.
Pich, G. (1937) *Beitr. path. Anat.*, **98**, 218.
Raynaud, A., and Frilley, M. (1947) *Ann. Endocr. Paris*, **8**, 400.
Rossi, E., and Caflisch, A. (1951) *Helv. paediat. Acta*, **6**, 119.
Russell, A., and Swyer, G. I. M. (1952) *Proc. R. Soc. Med.*, **45**, 596.
Ullrich, O. (1930) *Z. Kinderheilk*, **49**, 271.
Varney, R. F., Kenyon, A. T., and Koch, F. C. (1942) *J. clin. Endocrin.*, **2**, 137.
Wilkins, L., Grumbach, M. M., and Van Wyke, J. J. (1954) *J. clin. Endocrin.*, **14**, 1270.
Witschi, E. (1951) *Recent Progr. Hormone Res.*, **6**, 5.

Dr. G. I. M. Swyer: In a recent preliminary communication Wilkins *et al.* (1954) reported skin biopsy studies on 8 apparently female examples of "ovarian agenesis". In 6 of these, the chromosomal sex appeared to be male but it was female in the remaining 2. Thus, the findings of Polani *et al.* (1954) are confirmed, and Dr. Russell's general thesis is amply supported. At the same time the obvious possibility that some at least of these patients with gonadal agenesis are of female chromosomal sex becomes a certainty.

References

Polani, P. E., Hunter, W. F., and Lennox, B. (1954) *Lancet*, ii, 120.
Wilkins, L., Grumbach, M. M., and Van Wyke, J. J. (1954) *J. clin. Endocrin.*, **14**, 1270.

Dr. Russell (in reply): According to the thesis we outlined in 1952, failure of sexual maturation of the primitive gonadal anlage, as in "gonadal agenesis", could probably arise in *either sex*. Nevertheless, that it can indeed occur in genetic females as well as in males cannot be accepted by us as "a certainty" unless the internal genital status and absence of ovaries in cases cited have been exposed unequivocally at laparotomy. I have already emphasized how readily errors can creep in when accepting the absence of ovaries on clinical criteria alone. Unfortunately, Polani *et al.* (1954) also failed to cite laparotomy proof of gonadal and internal genital status in the 3 cases of "Turner's syndrome" they studied by skin biopsy, ranging in age from 10 to 20 years.

If the "ovarian agenesis" of the 2 cases of Wilkins *et al.* (1954) presenting female sex chromosomes has indeed been established at laparotomy then we gladly acknowledge the implications of their findings, and would accordingly adjust diagnostic interpretation of chromosomal typing in the webbing syndrome. The diagnostic issue is of some importance: although male "typing" by a simple leucocyte examination would still have positive screening value as already outlined, female chromosomal typing would then afford no help in deciding between gonadal agenesis or not.

Steatorrhoea with Osteomalacia, Amenorrhœa and Absent Body Hair.—ARNOLD BLOOM, M.D., M.R.C.P.

Mrs. R. M., aged 26.

History.—One of five siblings, others in good health. Active at school, played games, never ill.

Aged 14, developed large ulcers on both shins, which persisted until a year ago.

Married five years, one miscarriage. For the past four years, periods scanty or absent; amenorrhœa six months.

Eighteen months ago weight 8 st. 9 lb.; appetite became poor, developed intermittent diarrhœa, several loose motions daily. Bedridden for nine months prior to admission.

On admission.—Weight 5 st., wasted, helpless, ulcerated back, skin pale and smooth, absent pubic and axillary hair, genitalia and legs œdematous (Fig. 1). Marked tetanic

FIG. 1.

FIG. 2 (3.9.54).—Triradiate pelvis with fractures of pubic rami.

FIG. 3 (11.11.54).—After therapy. Callus formation at fracture sites.

spasm of arms and hands, Chvostek's sign positive. B.P. 90/50. Her manner was childlike, with cheerful indifference to her plight.

Findings.—Serum calcium 6, phosphorus 3·4, sodium 305, potassium 17·5, cholesterol 130, urea 15 mg./100 ml.; total serum proteins 3·3 grams%; alkaline phosphatase 36·1 K.A. units; Hb 67%; mild iron deficiency anæmia. Blood sugar curve 86 fasting, 86 half an hour after ingestion of 100 grams glucose, 82 one hour after, 68 mg./100 ml. two and a half hours after. Total fæcal fat 36·6 grams/100 grams fæces. Of the fæcal fat 90% is split. Fat balance (three days 100 grams fat/*diem* intake) 86% absorption. Urine: calcium not present; amino acids increased; 17-ketosteroids 0·7 mg./24 hours. F.S.H. (Dr. Russell Fraser) 8 mouse units positive, 16 mouse units negative.

X-rays: Generalized rarefaction of all bones; pelvis triradiate due to pressure of femoral

heads on softened bones; Milkman fractures in ribs, left fibula (two) and both pubic rami (Fig. 2).

Treatment and progress.—Intravenous calcium gluconate. High protein, gluten-free diet. Ergosterol 600,000 I.U. intramuscularly every two weeks, folic acid 10 mg. t.d.s., Becosym tabs. 2 t.d.s. and ascorbic acid 50 mg. t.d.s.

Early relief of tetany and slow general improvement. No diarrhœa. Despite loss of œdema, weight rose by 5 lb. Able to walk, though with limp.

Blood calcium rose to 10·4 mg.%, serum protein to 5·4 grams %. Repeat X-rays after six weeks showed generalized increase of bone calcification and callus formation at fracture sites (Fig. 3).

Comment.—The endocrine depression, as evidenced by amenorrhœa, absent body hair and low 17-ketosteroid excretion, is probably due to severe malnutrition. The normal urinary F.S.H. secretion suggests that the pituitary gland is not primarily at fault.

In view of her steady improvement on present lines, no adjuvant endocrine therapy has as yet been tried but the low serum protein and low 17-ketosteroid excretion make it likely that osteoporosis is present as well as osteomalacia.

BOOKS RECENTLY PRESENTED AND PLACED IN THE SOCIETY'S LIBRARY (*Continued from page 312*).

Douady (D.). Les sanatoriums universitaires français. pp. 222. Paris: Sirot. 1952.

Harkness (A. H.). Non-gonococcal urethritis including the genital manifestations of local and systemic diseases and infestations of the urinary tract with protozoa, metazoa and fungi. pp. 424. Edinburgh: Livingstone. 52s. 6d. 1950.

Hartmann (G.), and Schulsinger (F.). Physical and mental stress and consequential development of atherosclerosis within the Jewish population of Denmark. pp. 78. Copenhagen: Rosenkilde & Bagger. 1952.

Injo Beng Liong. De Tuberculine reactie. pp. 203. Batavia: Keng Po. 1940.

James (W.). The varieties of religious experience: a study in human nature, being the Gifford lectures on natural religion delivered at Edinburgh, in 1901–1902. pp. 534. New York: Longmans. 1902 (Reprint 1912).

Janet (P.). Les obsessions et la psychasthénie. Paris: Alcan. Vol. **2,** 3rd edit., 1919; Vol. **3,** 2nd edit., 1911.

Jong-Martis (W. de). Congenitale syphilis bij inheemsche en Chineesche zuigelingen. pp. 234. Batavia: Kappee. 1937.

Kinget (G. M.). The drawing-completion test: a projective technique for the investigation of personality. pp. 238. New York: Grune & Stratton. $6.75. 1952.

Koch (C.). The tree test: the tree-drawing test as an aid in psychodiagnosis. pp. 87. Berne: Huber. 1952.

Lammerts van Bueren (B.). Bacillaire dysenterie bij kinderen te Batavia. pp. 204. Batavia: Olt. 1939.

Landouzy (L.-T.-J.), and Bernard (L.). Éléments d'anatomie et de physiologie médicales. pp. 765. Paris: Masson. 1913.

Loe Ping Kian. Syphilis en zwangerschap. pp. 314. Batavia: Keng Po. 1941.

MacKenna (R. M. B.), ed. Modern trends in dermatology. pp. 432. London: Butterworth. 42s. 0d. 1948.

MacKenna (R. W.). Diseases of the skin: a manual for students and practitioners. By Robert M. B. MacKenna. With a chapter concerning radiology by I. G. Willian s. 5th edit. pp. 607. London: Baillière, Tindall & Cox. 42s. 0d. 1952.

Mansvelt (J. van). Pick's disease. pp. 312. Enschede: M.J.v.d. Loeff. 1954.

Naumburg (M.). Psychoneurotic art; its function in psychotherapy. pp. 148. New York: Grune & Stratton. 54s. 0d. 1953.

Percival (G. H.), Drennan (A. M.), and Dodds (T. C.). Atlas of histopathology of the skin. pp. 494. Edinburgh: Livingstone. 75s. 0d. 1947.

Section of the History of Medicine

President—Sir ZACHARY COPE, M.S., M.D., F.R.C.S.

[*January* 5, 1955]

William Clift, F.R.S.

First Conservator of the Hunterian Museum

By JESSIE DOBSON, B.A., M.Sc.

(*Recorder of the Museum, Royal College of Surgeons*)

WILLIAM CLIFT, the youngest of the seven children of Robert Clift, a miller, and his wife, Joanna, was born at Burford Mill, just outside Bodmin in Cornwall on February 14, 1775. He was only 9 when his father died and the family, then in poor circumstances, moved to a small house in Castle Street, Bodmin. Mrs. Clift and the older children worked in the fields in the summer and carded wool in the winter to provide even the barest necessities, but William, a promising scholar, was kept at school in spite of the sacrifices that this entailed. He excelled in drawing and penmanship and augmented the family income by writing signs and notices for shopkeepers.

At the lower end of Castle Street, opposite the church, is the "Priory", then the residence of Colonel and Mrs. Gilbert. It was in the kitchen of this house that William used to play when he was a small boy and it was in the stream running through the grounds that he was taught to fish by his schoolmaster. After the death of his mother, however, in 1786, his schooldays came to an end and work was found for him in a market garden. This did not last long for his master, Mr. King, was not well pleased when he found a caricature of himself executed by his youngest employee. Then followed several years of casual work until the day when he was invited by Mrs. Gilbert to consider taking employment in London. Mrs. Gilbert had been a schoolfellow of Anne Home who, in 1771, had married John Hunter, and the two ladies had maintained their friendship. It was in the autumn of 1791, when Colonel and Mrs. Gilbert were on a visit to London, that Hunter mentioned that since William Bell, his amanuensis, had left him to take the post of surgeon at Bencoolin in Sumatra he had been unable to fill the post to his satisfaction. Mrs. Gilbert recommended young William Clift as being suitable and so the affair was settled. The documents of apprenticeship were prepared by Mr. Brown, the Bodmin lawyer, Colonel and Mrs. Gilbert supervised the arrangements and early in 1792 the boy set off by sea from Fowey on his great adventure. He arrived at 28, Leicester Square on his own and John Hunter's birthday, February 14. Hunter was ill at the time so Clift spent the first few days in making himself acquainted with the premises. The main house faced the square; in the open space behind it Hunter had built his museum and lecture rooms. A smaller house faced Charing Cross Road, then known as Castle Street, and it was here that Clift and the resident pupils had their apartments. Among the pupils at that time were Philip Syng Physick, soon to return to America to become one of its leading surgeons; Francis Kinloch Huger who, two years later, was to join in the attempt to rescue Lafayette from imprisonment at Olmutz; and Pierce Smith who, in 1794, was "seen in Paris carrying a revolutionary flag at the head of one of those horrible and sanguinary French Liberty and Equality mobs" and probably lost his life then, for nothing further was heard of him.

Soon Clift settled down to the routine he was to follow for the next eighteen months and maybe the arrangement was ideal in that Hunter was the more disposed to take pains with the training of a protégé of Mrs. Gilbert's and his apprentice was only too anxious to give satisfaction in order to please his patroness. The day began at 6 in the morning when they worked together in dissecting and preparing new specimens for the museum. Clift then wrote out the visiting and engagement lists for his master and, during Hunter's absence, wrote notes on the new preparations and finished the dissections. In the afternoon he had a drawing lesson and at about 6 in the evening he joined his master again for the evening's work of answering correspondence, sorting and arranging the new descriptions for the catalogue and recording cases. At the weekend the routine only varied in that the work was carried out at Earl's Court, Hunter's country house. It was a full, busy life and one that particularly appealed to the young boy for each day he was acquiring fresh knowledge and skill. Hunter soon expressed himself pleased with his progress and the rigid method of work instilled into him in these early days made him retain to the end of his life the same conscientiousness in performance and devotion to duty. The bond that grew between them was one never to be broken and it was small wonder that Hunter's sudden death on October

16, 1793, was such a tragic event to him. He had lost his guide and protector, and it was not to be expected that Everard Home, Hunter's brother-in-law, or Matthew Baillie, his nephew, would have the same personal interest in his welfare. Added to his grief at losing a kind and considerate master was the fear that his services might no longer be required for, at the age of 18, he was ill-equipped for any other occupation, half-trained as he was in the one that he had come to enjoy. He had early realized, however, that the museum was his master's greatest treasure and that, unlike other museums of that period, it was not merely a collection of rare and curious objects but was an ordered arrangement of specimens each of which was an essential link in the story. If the sequence was broken, the whole significance was lost. So, for the next seven bleak and lonely years, when there was no one to advise or teach him or give praise for work well done, he never relaxed his care and when, in 1799, the museum was bought by the government and handed to the custody of the newly constituted Royal College of Surgeons, the preparations were in as perfect a state as when Hunter was alive.

It was at Christmas in that year that Clift was informed by the Board of Curators that he had been appointed Conservator and just over a year later he married Caroline Harriet Pope at St. Martin-in-the Fields. For the first six years of the new century the collection remained in the Castle Street premises until the new buildings, designed by George Dance, on the south side of Lincoln's Inn Fields should be completed. It was while the building was in progress that Clift suggested to the architect that the front of the College would receive better illumination if the lamps had glass tops rather than the tin ones previously used. His idea was adopted and was soon in general use all over the city. Apartments in the College were assigned to Mr. and Mrs. Clift and their two children, William Home and Caroline Amelia. The square in those days was a pleasant residential area. Henry Cline, who attended Edward Gibbon in his last illness and who served on the Court of Assistants of the College for almost thirty years, resided there. It is said that each year on November 5, he celebrated the acquittal of John Horne Tooke from the charge of high treason in 1796. Sir John Soane, the architect, lived in the house opposite the College, now his museum, and Spencer Perceval, the politician, was a resident until 1807 when he was appointed Chancellor of the Exchequer.

The removal of the specimens from Castle Street brought many anxieties and problems but Clift felt amply repaid for his years of devoted care when he saw the collection arranged in the handsome new building. It was indeed a pleasure to him to conduct the hundreds of distinguished visitors round the museum, but he was especially proud to perform this duty on May 25, 1811, when Mrs. Hunter and her daughter, Mrs. Campbell, visited the College.

Clift found that he had many new duties quite apart from the general care of the museum. One of these was to dissect the bodies of those who had been hanged for criminal offences. Perhaps the most interesting of these was John Bellingham who assassinated Spencer Perceval, then Prime Minister, in 1812. Bellingham had been arrested in Russia for some misdemeanour and, on his return to England, appealed for redress. His plea being ignored, he shot the Prime Minister as he entered the House of Commons on May 11. Bellingham was hanged a week later at Tyburn, and when Clift received the body he observed that the heart was still beating.

Having arranged the museum in its new quarters, Clift devoted more of his time to the continuance of his studies. Hunter had pointed the way and the goal but it was Clift's perseverance that made him attain it. He taught himself French and German and began to build up a library of scientific and other works. He attended meetings, including those of the Anatomical Society, founded in 1796, that met at the Freemason's Tavern in Great Queen Street; the Geological Society, founded in 1807, and, later, the Zoological Society. He devoted much time to the education of his two children and with them learned to play the piano and other musical instruments. He acquainted himself with the progress of the arts, and attended plays and operas. The work of the great poets, Keats, Shelley, Wordsworth, Southey and Byron was becoming popular. Clift probably followed the career of Byron with particular interest, knowing that Hunter had examined his malformed foot soon after he was born and had, some years later, recommended a certain type of footwear to correct the deformity. This was the hey-day of the great painters, Romney, Constable, Lawrence, Stubbs, Turner; Clift had in his library Landseer's treatise on Engraving and Calcott's and Da Vinci's works on Painting. It was not surprising, therefore, that he often worked far into the night to accomplish all the tasks he set himself.

These were stirring times, not only in Clift's life but in the Western World generally. Many of the wounded heroes of naval battles presented themselves at the College to have the severity of their disabilities assessed for purposes of pension. One of these was Lieutenant John Ross, who, some ten years later, when increasing world trade made manifest the desirability of finding a "north-west passage", was one of those who led an expedition for this purpose. Clift took advantage of this and sent on board the "Isabella" boxes containing

spirit-filled bottles, with instructions for the preservation of any interesting specimens of natural history that might be found.

Certain events stand out in this period. The year 1819 saw the death, at the age of 73, of Clift's good friend and benefactress, Mrs. Gilbert. In the following year he went with his daughter to Paris and, in addition to visiting museums and meeting fellow scientists, he saw Talma, the great actor, friend and protégé of Napoleon, in the role of Hamlet. Napoleon died on May 5 and the unfortunate Queen Caroline, consort of George IV, on August 7, 1821; and this year was made memorable for Clift by the death of Mrs. Hunter, who had never lost interest in the welfare of her husband's last pupil. It was in 1823 that Clift received the highest reward for his long years of toil. In January he was greatly pleased by his son's appointment as Assistant Conservator; and in May he himself had the honour of being elected a Fellow of the Royal Society. The poor little boy from Castle Street, Bodmin, had indeed travelled far. This recognition of his worth by his associates was no more than he deserved but it was none the less gratifying.

But it was also in 1823 that he had to suffer what was probably one of the severest blows of his life. While travelling together to Kew, Sir Everard Home informed him that he had burned John Hunter's manuscripts. Pleasing and exciting as the events of the last twenty years had been, ever first and foremost in Clift's mind was his concern for the museum; and the destruction of these documents meant that some of its value was irrevocably lost. He now realized what good service he had done by copying out many of Hunter's notes for his own information during the years following Hunter's death until the papers were removed to Home's own house in 1800. After many difficulties and delays, arrangements were made to remedy the loss so far as possible. In 1827, Richard Owen was appointed Assistant Conservator and both he and Clift's son set to work to assist in the preparation of catalogues, an undertaking that Everard Home had engaged to perform but had never carried out. This formidable task was still in progress when William Home Clift died as the result of an accident in 1832, the year that also saw the death of Everard Home.

After several years of collaboration with Clift, Owen was able to assume the more arduous duties connected with the care of the museum. We have no evidence whatever that Clift was other than friendly and appreciative of Owen as a colleague or as a prospective son-in-law. We do know, however, that Mrs. Clift for many years refused to consent to his marriage with her daughter and it was not untill 1835 that the event took place. In 1834, Clift brought to the notice of the Board of Curators the fact that the accommodation was no longer adequate to house the collection, materially extended as it had been by his own efforts and by numerous donations and purchases; and the museum was closed until 1837 for reconstruction. In 1840 further help in maintaining the collection was provided by the appointment of students who assisted in showing visitors round the museum and in preparing new specimens, under Clift's supervision. One of the earliest of these was John Thomas Quekett who was to succeed Owen as Conservator. It is from Quekett's diaries that we learn that Owen was not always easy to work with, a fact that became more apparent in later years when his frequent dissensions with the Council led to his resignation in 1856.

In 1842 Clift, now aged 67, considered that he was no longer able to carry out to his satisfaction the multifarious duties of conservator and it was decided that Owen should now take over this post. Mr. and Mrs. Clift vacated the apartments in the College that they had occupied so happily for the last forty years and they made their home at Stanhope Cottage, Regent's Park. For the next seven years, apart from occasional visits to the College, his greatest pleasures were to tend his garden and enjoy the company of his grandson, William Owen. The death of his wife, his loving companion for nearly fifty years, seemed to cause a serious decline in his own health and he died only three months later, on July 16. 1849.

So ended the life of a most admirable man, one who was always ready and willing to help those anxious to learn, and who was never daunted by difficulty or disappointment. He possessed those fine virtues, loyalty and courage: loyalty to John Hunter's memory; and courage that made him fight for his master's most cherished possession. It is not due to Owen, Quekett, Flower or the many other famous men who have held the post of conservator, great though their individual achievements have been, that we still have this collection that reveals the genius of John Hunter. Clift set the example that they followed. It was Clift who, in sole charge for the seven years following Hunter's death, when a few weeks' neglect would have ruined the whole collection, never once relaxed his care. It was Clift who for the next forty-two years fought for its preservation as Hunter had arranged it and was constantly on his guard against those, like Everard Home, who had their own ideas about its ordering. He never gave way and it is due to his single-minded devotion that John Hunter's unwritten book, his museum, has been preserved. Some of the pages may be difficult to read, for the collection was sadly depleted in 1941, but the story is still there for those who choose to find it.

Isaac Buxton, 1773–1825

By NORAH H. SCHUSTER, M.A., M.B., Ch.B.

WHEN the Royal Chest Hospital was abolished in 1954 the Secretary of this Section had the kindly thought that its founder might be commemorated. So far as we know, it was the first chest hospital in the world and Dr. Buxton has never had any recognition of his achievement. I knew nothing about him, and I had not been long at work before I came upon some very damaging reflexions on his character, mostly in E. W. Morris's *History of the London Hospital* (2nd edit., London, 1910). By the courtesy of Mr. L. W. Wilding of that hospital, I was able to look into all the records and I came to the conclusion that their historian had been both harsh and inaccurate about Buxton. Some of the statements are matters of opinion but some relate to historical fact and, as an example, I will just take Isaac Buxton's place in that great family which Morris denied him. There is not the slightest doubt that he belonged to it and quite possibly the first John Buxton to take an interest in the London Hospital in 1741 was his own grandfather.

Isaac's birth on May 6, 1773, was registered at Dr. Williams' Library and he was born in Grange Walk, an interesting street which contained the remains of Bermondsey Abbey and still has a few antiquities. When he was 9 years old he went as a Foundation Scholar to St. Paul's School and afterwards he was apprenticed for five years to his brother-in-law, Mr. Wrench, a seed merchant. But the period 1790–1800 is rather a mystery. According to the Authentic Memoirs of the Royal College of Physicians which was published during his lifetime (1818) he practised for a time as a dissenting minister but I can find no corroboration of this in Nonconformist records.

He was 27 before he went to Göttingen in 1800 to read medicine. The medical school at that time was attracting students from all parts of Europe, and the most powerful magnet was J. F. Blumenbach, Isaac Buxton's tutor. In 1802 he obtained his doctorate with a thesis which seems to have been a study of man as a ruminant, inspired possibly by the prevailing enthusiasm for comparative anatomy at Göttingen (Fig. 1). He also took the Oath.

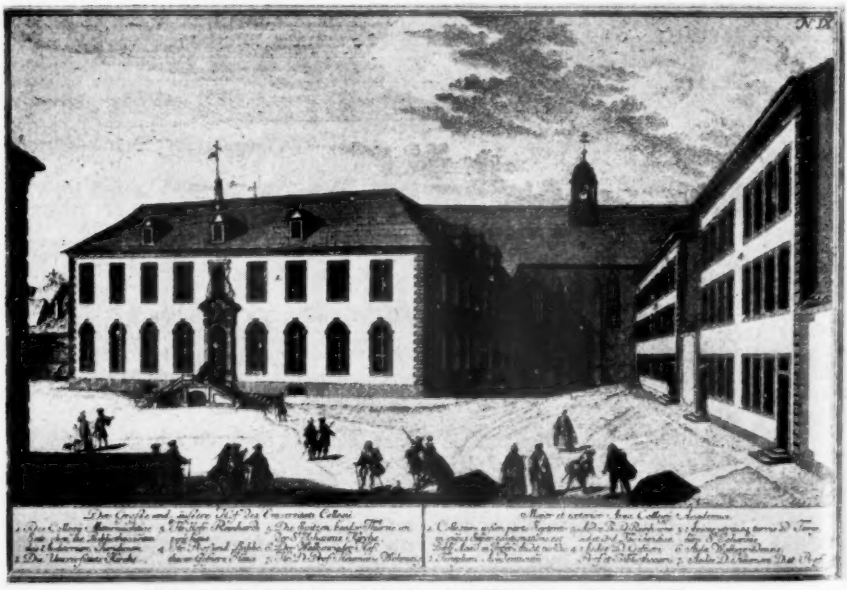


FIG. 1.—Georgia Augusta University, Göttingen. Opened 1737.

There were several styles of Oath in the medical schools of Europe; most of them were quite brief and omitted many of the provisions of the true Hippocratic Oath even in its Christian form. The one of Göttingen had an unusual clause which required a doctor of the town to denounce to the authorities any case of wounding to which he was called. It may have been part of an attempt to stop indiscriminate brawling as a few years before students had

been forbidden to wear their swords and even the three English Princes had had to conform to the rule when they were at the University, about 1788. In 1802 Buxton returned to London and enrolled at Guy's as a pupil dresser to Astley Cooper, and in 1805 he obtained the Licence of the Royal College of Physicians (Fig. 2).

In the next year he was on the staff of the Surrey Dispensary, the most important, if not the only, dispensary south of the river. The Apothecary kept an attendance book much to the annoyance of the doctors, but Buxton comes well out of it and several times "No rowdiness" was recorded of his clinic.

A year later he got on the staff of the London Hospital. There was no trick about his election as stated by Morris. It was just one of those battles inseparable from hospital appointments of the time and the London itself had others of a similar nature.

Then came a period of successful practice mostly in New Broad Street, during which time he married Janet Travers, first cousin to the surgeon Benjamin Travers, and promoted the little hospital for chest diseases in Spitalfields.

There is nothing to indicate whether he ever used a stethoscope but he could just have been aware of it before he retired in 1822. He knew French and both his successors at the Infirmary were enthusiastic followers of Laennec, so he was quite possibly interested in the instrument, especially as he is known to have been enterprising and once advised a young man never to condemn a new idea however mad it might seem at first sight.

He must have been fairly well thought of by his colleagues as he was elected to the Hunterian Society Council in its second year, but his health was failing and he attended no meetings. In 1822 he had to give up all his work and resign from the London. The scandal was to do with an anonymous report to the Governors that he had resigned for a pecuniary consideration. There is plenty of evidence that he resigned simply for ill-health and he died three years later. If he negotiated for the goodwill of his appointment together with his practice he was doing no more than was customary at the time and for many years afterwards.

He died in Camberwell in 1825 and was buried in Bunhill Fields, and except for the calumnies already mentioned he has rested in obscurity ever since.

Buxton can claim three achievements worthy of mention:

(1) An Essay written in 1810, a copy of which is in the Royal Society of Medicine;

(2) A set of statistics of London Hospital Admissions from its earliest days until 1820 which is in the library of the Royal College of Physicians;

FIG. 2.—Isaac Buxton, 1773–1825.

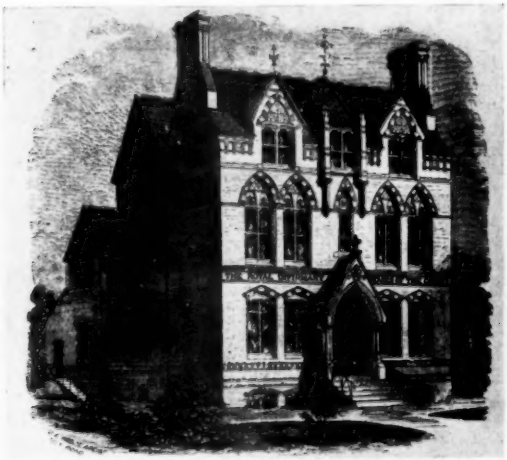


FIG. 3.—Royal Chest Hospital; first building in City Road, 1863.

(3) The foundation of the Infirmary which afterwards became known as the Royal Chest Hospital.

(1) One of Buxton's principal enthusiasms was the heating of sick rooms. He aimed at a temperature of 60° to 65° F. night and day during the winter months for patients with any kind of cough or consumption. It was not an original idea: Nottingham Hospital already had some central heating and the London was planning it. Beddoes was one of those who had written on single room heating but he had confused the issue with his cow-

house emanations, and Buxton was the first to make really practical suggestions for ordinary sick rooms.

His Essay is exceptionally well written; there are some statistics on the relation of climate to pulmonary diseases, a few case histories (one of them sent by Jenner) and a survey of heating systems at home and abroad. I do not know what reception it had in medical circles here but it was abstracted in a French journal and it has been quoted in at least two standard engineering books on the history of heating and ventilating. Ventilation was an essential part of Buxton's proposals as he had experienced its deficiency in Germany.

(2) In the years 1817 and 1818 fever raged in the East End and the staff and governors of the London were very perturbed at the number of cases being admitted to the Hospital. Buxton undertook to go through the records of the previous seventy years and give them a picture of the trend of disease and his report was printed. It consists of Tables of Medical and Surgical Admissions arranged in different ways to bring out special points, with comments. The analysis showed that though there had been a true increase of fever cases during the two years in question relative to that ten-year period, yet they were fewer than in previous decades and there had been a steady decline over the whole series. Buxton attributed this to improved hygiene of the streets and houses in London. But in spite of the decline in the incidence of fever there was a relatively higher mortality in the later years and he attributed that to the late stage of illness at which patients were admitted through the reluctance of the authorities.

Another disclosure was that fever admissions covered all the fever cases in the hospital, and therefore neither patients nor staff caught it in the wards. This said a good deal for the hygiene of the London as at another institution as many as 35 out of 39 contracted fever after admission.

Buxton ended up modestly: "The reasoning I have presented may not be deemed conclusive; the facts however are preserved and they will remain whatever may be the fate of my arguments."

This laborious and useful work is not mentioned in any biography of Buxton; the London Hospital does not possess a copy of it or of any of his publications.

(3) The story of the Royal Chest Hospital must be limited to its foundation. On March 25, 1814, there was a great concourse of important people at the London Tavern, Bishopsgate, to inaugurate the new charity. Dr. Buxton explained that his principal purpose was to have an institution where the wards could be kept at a constant warm temperature during the winter and the two Royal Dukes of Kent and Sussex enjoyed themselves describing their sufferings with bronchitis and asthma when the weather was inclement. It was called the Infirmary for Asthma, Consumption and other Pulmonary Diseases, and for the first six years Buxton was the only physician. He did not segregate consumptives as has sometimes been said, but admitted every kind of chest complaint into his 8 beds.

A house was found in Union Street, Spitalfields, which had belonged to a silk merchant. It was an exciting neighbourhood. The house next door was the childhood home of William Allen, known as the Spitalfields Genius, and the first of that family in Allen and Hanbury. A few doors away was another celebrity, Peter Bedford, the Spitalfields Philanthropist, who specialized in juvenile delinquents. Near-by in Crispin Street, was the Spitalfields Mathematical Society composed mostly of working weavers, and in the interstices of all this beneficence, in the stinking courts and alleys, were the poorest of the poor of London, Isaac Buxton's patients.

One would not have expected such a worthy charity to arouse any opposition, but it did. Dr. Thomas Sutton, an Army surgeon of considerable repute, wrote six long letters to the Duke of Kent protesting at his patronage of the new foundation. They had been refused by a newspaper and were printed as a tract. The gist of Sutton's objections was that heated rooms had not been proved to be a cure for consumption, and that the poor would suffer all the more when they got back to their miserable homes.

The Infirmary was in Spitalfields for thirty-five years and then in 1849 it was transferred to the City Road (Fig. 3). It was badly damaged by a bomb in 1941 but carried on a busy Out-patient department until it was abolished in 1954.